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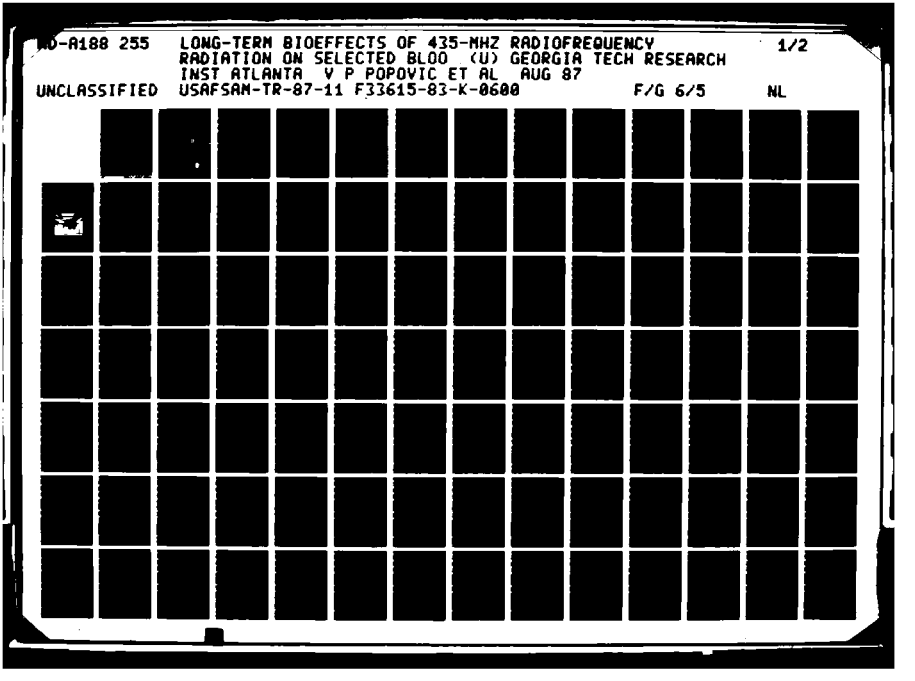

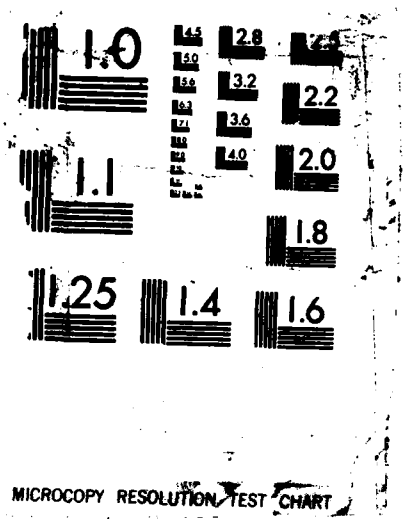
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LONG-TERM BIOEFFECTS OF 435-MHz RADIOFREQUENCY RADIATION ON SELECTED BLOOD-BORNE ENDPOINTS IN CANNULATED RATS

Volume 4. Plasma Catecholamines

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NOTICES

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The animals involved in this study were procured, maintained, and used in accordance with the Animal Welfare Act and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources-National Research Council.

The Office of Public Affairs has reviewed this report, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This report has been reviewed and is approved for publication.

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Two hundred adult male white rats (Sprague-Dawley) with chronically implanted aortic cannulas were randomly divided into two groups. Animals in the first group were exposed to low-level (1.0 mW/cm²) pulsed-wave 435-MHz radiofrequency radiation (RFR) for about 22 h daily, 7 days each week, for 6 months. Animals in the second group were maintained under identical conditions but were not radiated. The aortic cannulas were used to draw microsamples (0.6 mL) of aortic blood from the unrestrained, unanesthetized rats on a cyclic schedule. Plasma catecholamine (norepinephrine, epinephrine, and dopamine) concentrations were determined by radioimmunoassays. Statistical analysis of the results did not indicate increased plasma catecholamine concentrations in radiation-exposed animals when compared to sham-exposed animals. Exposure to this nonionizing radiofrequency (RF) environment did not induce stresses that were manifested as an alteration in plasma hormones.

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I. INTRODUCTION

During the past 50 years, the United States has witnessed a period of explosive growth in the radar and communications fields. This growth has increased the demand for available bandwidth and thus has pushed radar and communications frequencies into higher and higher ranges. Higher frequency ranges have permitted faster data transmission rates and reduced intersystem electromagnetic interference. However, these advances have come at the expense of altering the planet's radiofrequency radiation (RFR) environment. Until the advent of advanced radar and communications, cosmic rays and background radiation were the primary sources of the Earth's electromagnetic environment. Radar and communications transmissions have since increased the electromagnetic background or ambient radiation at the planet's surface by several orders of magnitude. At this time, the biological effects of exposure to this omnipresent electromagnetic environment are not well understood, despite studies conducted over the past several decades.

This report presents the results of plasma catecholamine (norepinephrine, epinephrine, and dopamine) assays of blood samples drawn from a large population of male Sprague-Dawley rats exposed to a 1.0 mW/cm^2, 435-MHz pulsed-wave (1.0 μs pulse width, 1-kHz pulse rate) RFR environment for a 6-month duration. The exposure group consisted of 100 cannulated rats housed in Plexiglas cages arrayed on the tiers of a stacked, parallel-plate circular waveguide. Engineering aspects of this waveguide and the exposure environment it generated have been previously reported [1]. The sham-exposure group consisted of 100 cannulated rats housed in an identical, but unenergized, collocated facility. Results reporting blood chemistry and hematology in these same animals will be published in the next volume of this series. Other volumes have already published results on adrenocorticotropic hormone (ACTH) and corticosterone [2] and prolactin [3].

The sympathetic-adrenal medullary system plays a critical role in the maintenance of cardiovascular and metabolic homeostasis. Plasma catecholamines have been measured to assess the functional activity of the sympathetic-adrenal medullary system under resting conditions or during stressful stimulation.

Norepinephrine, the neurotransmitter of the sympathetic nervous system, occurs in tissues of neural crest origin, sympathetic nerve endings, the adrenal medulla, and other chromaffin tissues as well as in the brain. Norepinephrine is synthesized from dopamine by the enzyme dopamine-β-hydroxylase [4]. The predominant sources of circulating norepinephrine are sympathetic nerve endings and the adrenal medulla. Both norepinephrine and dopamine-β-hydroxylase are secreted from sympathetic nerve terminals in proportional amounts during nerve stimulation [5,6] and can be accurately measured in the blood. This circulating norepinephrine derives largely from the sympathetic innervation to vascular walls--especially to small arteries and arterioles which provide the main source for peripheral resistance and therefore crucially influence blood pressure. The extent of norepinephrine "spillover" from the synaptic cleft to the general circulation depends on the cleft width: perisynaptic norepinephrine concentrations are relatively low for narrow gaps but high for wide gaps where the concentrations approach those estimated to be attained in the synapse. Since vascular intramural synapses have wide gaps, it seems likely that their proportional contribution to circulating norepinephrine is large when compared to nonvascular noradrenergic synapses such as in the vas deferens, which typically have narrow gaps. Thus the level of plasma norepinephrine reflects both adrenomedullary and sympathetic nerve activity.

The adrenal medullary responses were described first as endosecretory responses to stress. The release of epinephrine is part of this response and was first demonstrated in 1914 [7] in cats exposed to barking dogs. Similar responses occur after many psychological or physical stimuli. The release of epinephrine correlates with the degree of stress.

The physiologic functions of the dopamine receptors include vasodilation, increased sodium excretion, and increased myocardial contractility. Even change in the position (from standing on four legs to exploring the cage while standing on hind legs) is associated with enhanced sympathetic activity. Similar changes have been found in man by Sundin [8].

Exercise increases plasma catecholamines. High workloads or prolonged work stimulates several-fold increases in both norepinephrine and epinephrine concentrations. Many other stresses increase the release of catecholamines (particularly epinephrine and norepinephrine). Thus the plasma level of norepinephrine, epinephrine, and (to a lesser degree) dopamine fluctuates widely in a mammal reflecting increasing or decreasing physical activity or exposure to

various stressful environments [9]. The determination of catecholamine levels is used to quantitatively measure the level of stress induced on the autonomic nervous system. Sympathetic neuronal discharge, with adrenomedullary release of catecholamines into the blood, is a recognized component of the immediate physiological response to stress [7,10]. Even gentle handling produces an increase in epinephrine, whereas immobilization produces massive elevations of circulating levels of both epinephrine and norepinephrine. Decapitation or restraint lead to a 10-fold increase in circulating norepinephrine and an 80-fold increase in circulating levels of epinephrine, whereas dopamine increases to a lesser degree (Table 1). The high levels of plasma catecholamines in rats when compared with other animals and humans, and changes produced in pharmacological and physiological experiments, probably reflect environmentally induced changes in sympathoadrenomedullary activity rather than differences in basal sympathetic neuronal activity.

TABLE 1. CHANGES IN HORMONE LEVELS IN CANNULATED AND DECAPITATED RATS

	Cannulated			After decapitation		
Rat #	NOR	EPI	DA	NOR	EPI	DA
1	-	-	-	825	960	185
2	104	126	30	1275	2795	235
3	123	144	39	1740	1570	210
4	144	126	25	1870	3565	235
5	185	113	58	1435	2875	170
6	174	104	76	2660	5430	465
7	144	159	74	1170	1830	365
8	153	193	28	-	-	-
9	137	154	61	1425	2235	205
10	162	148	74	940	1345	260
11	144	177	43	1520	2975	255
12	-	-	-	1930	5295	440
$\bar{X}$	147	144	51	1526	2807	275
S.D.	24	28	20	515	1485	102

All hormone concentrations are in pg/mL.

II. MATERIALS AND METHODS

For this study, the concentrations of the plasma catecholamines norepinephrine, epinephrine, and dopamine were chosen as sensitive indicators of possible environmental stresses induced by RFR. To detect and quantitatively evaluate possible increases in plasma catecholamine levels induced by RFR, blood was sampled and assayed from 65 exposed and 64 sham-exposed animals (in the case of epinephrine); 63 exposed and 63 sham-exposed animals (in the case of norepinephrine); 64 exposed and 64 sham-exposed animals (in the case of dopamine). Analysis of the data obtained from the blood sample assays determined whether there were any RFR-induced changes in plasma catecholamine concentrations.

Animals. The rat represents a comparatively inexpensive and homogeneous population. For this reason, it is often desirable to use this species as the animal model in physiologic studies.

In this study, male Sprague-Dawley rats were used. All experimental animals were obtained from the same building and room at CAMM Research Labs, Wayne, New Jersey. The animals, weighing approximately 60 g, were delivered to Emory University where they were caged singly and given water and food (Purina Rat Chow) ad libitum. Temperature in the animal rooms was maintained at 24 $\pm$ 1 ^{o}C and the photoperiod was 12 hours/12 hours, with the lighted phase occurring between 8 AM and 8 PM.

Experimental Facility. The Georgia Tech Research Institute's Radiofrequency Radiation Facility [1] consisted of 8 collocated rooms on the basement floor of the Baker Building on the main campus. These 8 rooms provided a closed, complete facility for long-term bioeffects studies involving rodents.

The 100 exposure and 100 sham-exposure animals were housed in 2 identical, collocated rooms in the RFR Facility. Each room contained a stack of circular, parallel-plate waveguides fed by a slotted-cylinder antenna system for radiating the animals. The stacks of parallel waveguides consisted of five, 3.6-m (12 ft.) diameter plates that made up 4 sets of circular waveguides. Twenty-five individually housed rats were positioned around the circumference of each waveguide set. The walls of both rooms were lined with anechoic absorbing material and shielded with aluminum foil to prevent excessive microwave leakage radiation.

The circular, parallel-plate waveguide assembly provided a 1.0 mW/cm^2 exposure field around the circumference of the plates. The 45.7-cm (18 in.) plate separation distance permitted propagation of a TE_{10} mode wave with horizontal polarization. The power density displayed a cosine-squared dependency between the plates, with the maximum power density occurring midway between each set of plates. This arrangement positioned the electric field vector parallel to the rat's longitudinal axis, thereby maximizing the coupling between the electric field and the rat.

A slotted-cylinder antenna with the proper diameter, thickness, slot length, and slot width dimensions fed the stack of circular waveguides in a manner that provided an essentially constant electric field intensity in the azimuth plane.

Cages. The cages were constructed of clear Plexiglas, which was essentially RFR-transparent at 435 MHz. Clear (rather than colored) Plexiglas was chosen to permit visual observation of the rats. Each cage was 22.9-cm (9 in.) long by 12.7-cm (5 in.) wide by 17.8-cm (7 in.) tall. These dimensions complied with dimensions recommended by the National Institutes of Health for long-term housing of rats [11]. The food hopper and water bottle were placed on the distal side of the cage to minimize their interaction with the exposure field. The glass floor rods in the cage were oriented perpendicular to the cage's long axis to induce the rats to preferentially align themselves parallel to the electric field vector. The sipper tubes of the water bottles were made of glass to be nonperturbing in the field. Evaluations of the cages conducted in the circular, parallel-plate waveguide assembly showed field scattering from the Plexiglas to be below the range of detection.

The RFR Facility contained a data acquisition system for storing and processing experimental data, an electronic balance for weighing the rats during the study, and rooms for transmitter operation, blood sampling, cage washing, and materials storage.

To avoid the possible effects of noise during this study, the entire Radiation Facility was kept locked to avoid unauthorized entry. Only the animal caretaker and the technician who sampled blood from the animals were permitted uncontrolled entry to the Facility.

Cannulation. To detect and quantitatively evaluate changes in plasma catecholamines, the resting levels of these hormones first had to be determined. To obtain the real resting values of the three hormones in undisturbed animals,

many routine techniques for handling the animals and for sampling the blood were unsuitable for this study. For example, guillotine blood sampling techniques commonly employed in many endocrinological studies were immediately ruled out. To use each animal as its own control, arterial blood was sampled by means of chronically implanted aortic cannulas [12,13,14]. This simple, inexpensive technique permitted remote, stress-free blood sampling in conscious, unrestrained and resting rats. Arterial blood drawn through the resting rat's chronically implanted cannula was assayed for plasma norepinephrine, plasma epinephrine, and plasma dopamine.

The idea of sampling venous blood from the animals was abandoned. In venous blood vessels, the flow regime is laminar with blood flowing in discrete layers. The layers of blood in the middle of the vessels travel much faster than those close to the vessel walls. The most important consideration, however, was that blood layers do not mix in venous blood vessels. Thus, a sample of venous blood, withdrawn with a needle or a cannula, might represent the blood returning from one part of the body or the other, from a single organ or muscle, or from any one of the endocrine glands. For this reason, we decided to sample arterial blood, which is always fully mixed. The mixing occurs in the left ventricle of the heart and in early parts of the aorta. Only small amounts of arterial blood (up to 0.6 mL) were withdrawn from resting rats about once every 3 to 5 weeks. Removing greater volumes of blood has been shown to elevate plasma norepinephrine concentrations in the rats (Fig. 1).

We used PE-10 arterial cannulas in this study. Larger PE-50 cannulas were unsuitable because they could develop large blood clots if not drained frequently. Large cannulas require multiple flushing to remain patent, but flushing might induce multiple strokes in the animals. Chronic cannulation of the aorta with a PE-10 cannula was preferable to cannulation of other arterial blood vessels. Cannulation of the abdominal aorta provided long-term functional cannulas, but the cannulation procedure was lengthy (20-30 min) and required opening the abdominal cavity and temporary dislocation of the gastro-intestinal system. The abdominal aortic cannula had a much larger dead space than the aortic cannula. Cannulation of the aorta through the left carotid artery, on the other hand, required an incision of 1-1.5 cm that neither penetrated body walls nor entered the abdominal cavity. Further, this cannulation could be completed in about 8 min.

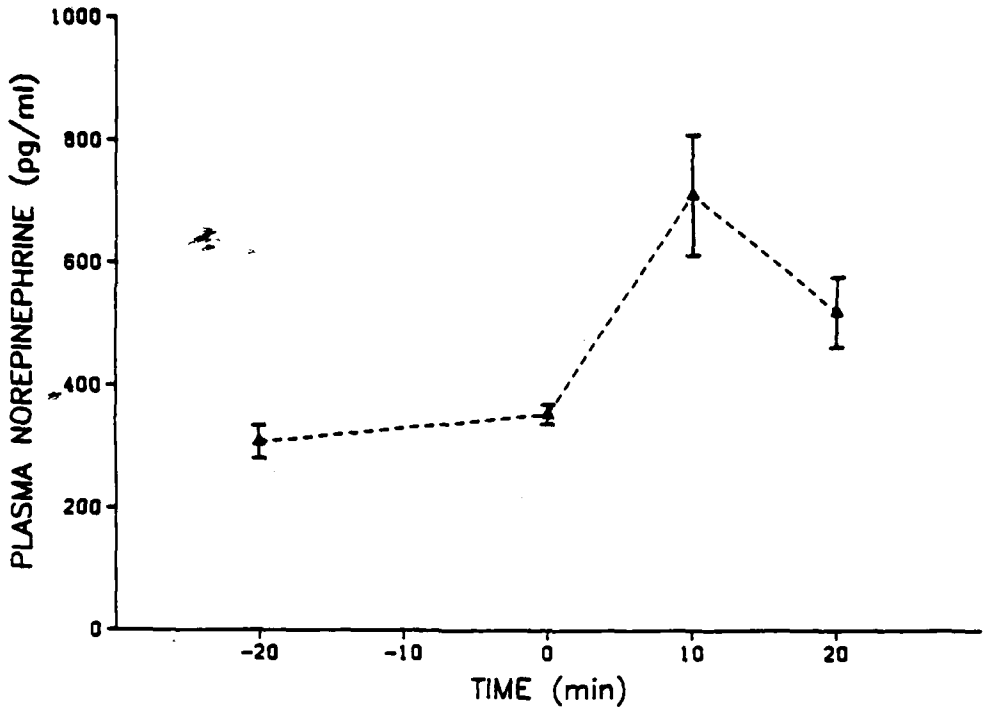

Figure 1. Effect of 1.0 mL bleeding on resting plasma norepinephrine concentration.

The carotid artery of the animal was cannulated 8 to 10 days before the animals entered the study. The surgery was done using ketamine-xylazine anesthesia (1:1 mixture; ketamine 100 mg/mL, xylazine 20 mg/mL, i.m. 0.1 mL / 100 g of body weight). The catheter was filled with slightly heparinized saline*, and the distal end was sealed with a nylon plug. Stress hormone levels returned to the basal values about 3 days after implantation of the chronic arterial cannulas. The first blood sampling occurred 10 days after aortic cannulation.

Blood Sampling. Although the half-life of plasma catecholamines is only 1 to 3 min [15], a strong stimulus leaves plasma catecholamine levels relatively high for a period of up to 15-20 min. Normal handling (lifting the rat) evoked a 75% increase in epinephrine concentration accompanied by a small increase in norepinephrine concentration. However, the animals had to be handled when they were removed from their exposure cage and placed in the "sampling box" in preparation for blood withdrawal. To avoid the undesired effects of handling on catecholamine levels, blood from the aortic cannula was sampled 30 min after the animal was placed in the sampling box. This procedure permitted the altered plasma catecholamine levels sufficient time to return to their basal (resting)

*0.5-cm^3 heparin sodium (from beef lung), 1000 units/mL per 30 cm^3 saline.

values. Each animal was preconditioned for the sampling box through a regime of several 30-min-long experiments conducted during a 1-week period before entering the study.

After acclimating for 30 min in the sampling box, the rat's cannula was positioned through the slot in the top of the box (Fig. 2). The heparinized saline was then removed from the cannula, and a 0.6 mL blood sample was taken from the resting rat using a sterile 1-cm^3 tuberculin syringe fitted with a 30-ga needle. The syringe and needle were rinsed with ethylene glycol-bis tetraacetic acid (EGTA)/glutathione before sampling. The blood sample was placed in an EGTA/glutathione-treated 1.0 mL capillary blood collection container (prepared in-house and stored under refrigeration to prevent chemical breakdown), shaken, and then placed on ice. The blood sampling procedure required about 2 min for each rat.

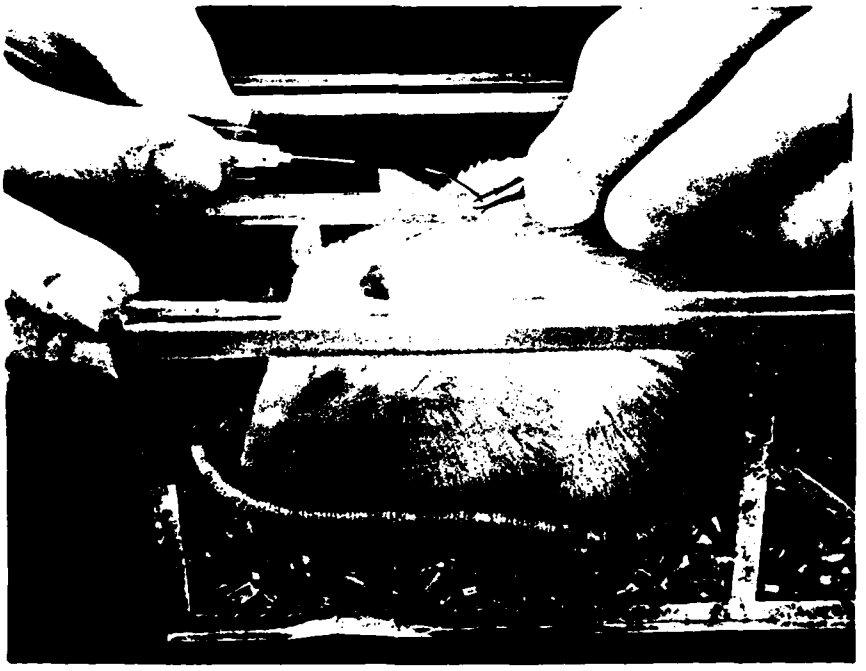

Figure 2. Sampling blood from the chronic aortic cannula of a resting, unrestrained, and unanesthetized rat.

Plasma catecholamine levels in conscious unrestrained rats with chronic indwelling catheters were considerably lower than previously reported for the rat [16].

Blood Sampling Schedule. Figure 3 shows the sampling schedule designed for the experiment. The 200 rats were introduced into the study in 4 groups of 50 animals each. The groups entered in a staggered manner to facilitate the process of logging-in and establishing the new animals. Each group contained 25 exposure and 25 sham-exposure animals. Of the 25 exposure (or sham-exposure) animals, 20 were sampled for plasma stress hormones, while the remaining 5 were used for hematology studies.

The sampling duration was 36 weeks long, including a 6-week preexposure adaptation period, a 24-week exposure period, and a 6-week postexposure period. With group staggering taken into account, the experiment duration was 42 weeks long (since introduction of the 4 groups was staggered in 2-week intervals). Plasma catecholamines were to be sampled for all periods marked (B) in Figure 3. Therefore, each animal should have been sampled for plasma norepinephrine, epinephrine, and dopamine at weeks -5, -2, 1, 4, 7, ..., 28. This schedule was rather rigorous and therefore could tolerate slight fluctuations in protocol without ill effects.

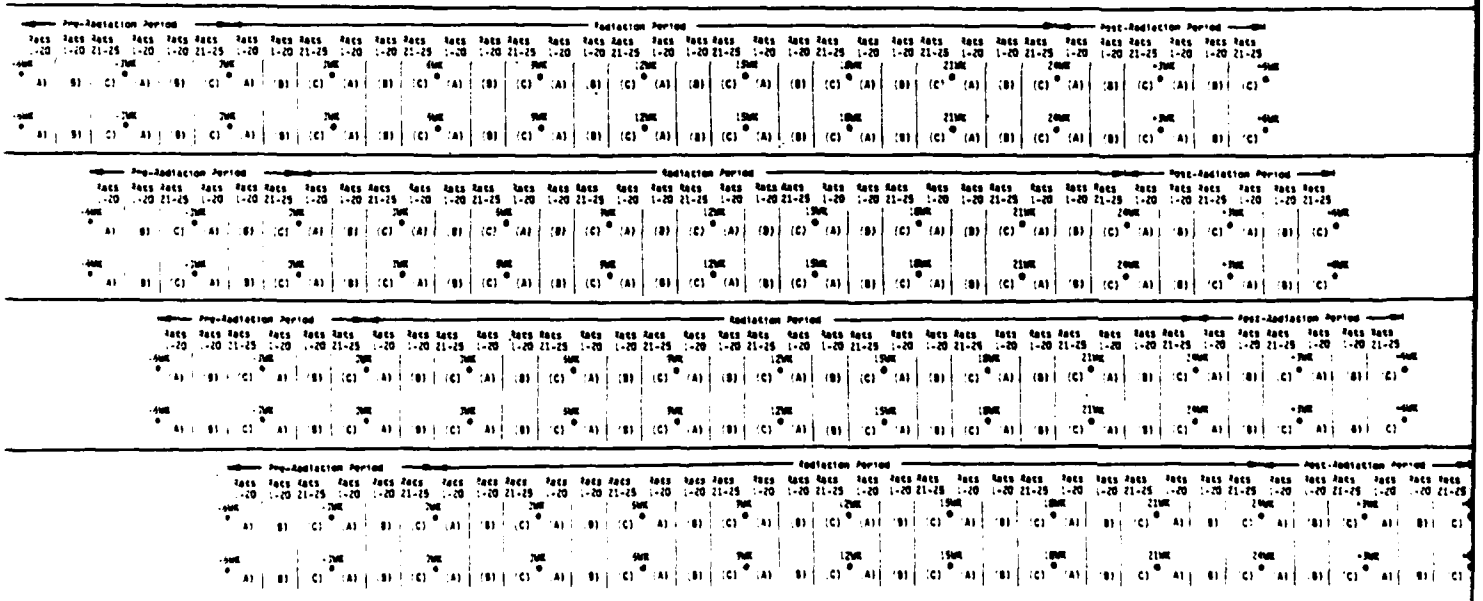

Figure 3. Sampling and exposure timetable.

Plasma Catecholamine Determinations. Plasma catecholamines were measured with a radioenzymatic method according to Penler and Johnson [17]. Briefly, the three catecholamines were first converted to their o-methylated analogues by catechol-o-methyl-transferase in the presence of S-adenosyl-methomine-^{3}H and thereafter extracted following addition of sodium tetraphenylbyrate. This extraction, together with an improved quick chromatographic separation and the oxidation of the epinephrine and norepinephrine derivatives to vanillin, yielded an extremely high sensitivity and specificity of the method. The assay allowed the determination of norepinephrine, epinephrine, and dopamine in plasma volumes of 20-100 µL.

III. RESULTS AND ANALYSIS

Plasma Norepinephrine. Appendix A contains the data collected during the preradiation and radiation periods for both the exposure and sham-exposure groups. The high variance displayed by the data for the entire sampling period indicated various degrees of animal activity at the time of blood sampling. Since the boxes had opaque walls, the activity of each animal before sampling was not recorded. However, as previously mentioned, it was unlikely that the stimulation of placing the rats in the sampling boxes had a major effect on resting norepinephrine concentration, since the increase in norepinephrine secretion induced by animal handling would disappear 20 to 30 min following the stress.

Figures 4 and 5 present the raw norepinephrine concentration in scatter diagram form (the dotted lines pass through the mean response at each week data were collected). Despite a 3-week effort to precondition the animals to the sampling box environment before drawing blood samples, the basal resting value of plasma norepinephrine decreased during weeks -3, -2, and 0. This same behavior was also observed in plasma ACTH, plasma corticosterone, and plasma prolactin [2,3]. After the first week, the data displayed a nearly linear response. The "spikes" occurring at weeks 10 and 17 (sham-exposure group) are the mean values resulting from 7 and 3 observations, respectively; the spike at week 11 (exposure group) is the mean value resulting from 5 observations. The wide range spanned by the 2-sided 95% confidence interval at each value indicated that these "spikes" may not represent drastic deviations from the established norepinephrine resting concentration. Noise and unfamiliar persons visiting the Radiation Facility may have also contributed to the sham-exposure group spike at week 10.

Mean plasma norepinephrine concentrations in the exposure and sham-exposure groups did not appear significantly different when plotted on the same axis (Fig. 6). This was preliminary evidence indicating that chronic exposure to 435-MHz RFR did not affect the resting level of plasma norepinephrine. A statistical analysis was subsequently performed on the data to test this hypothesis.

The analysis involved using multiple linear regression techniques to build a model describing plasma norepinephrine levels as a function of time and incident RFR. Terms of the polynomial model thus obtained were tested for their

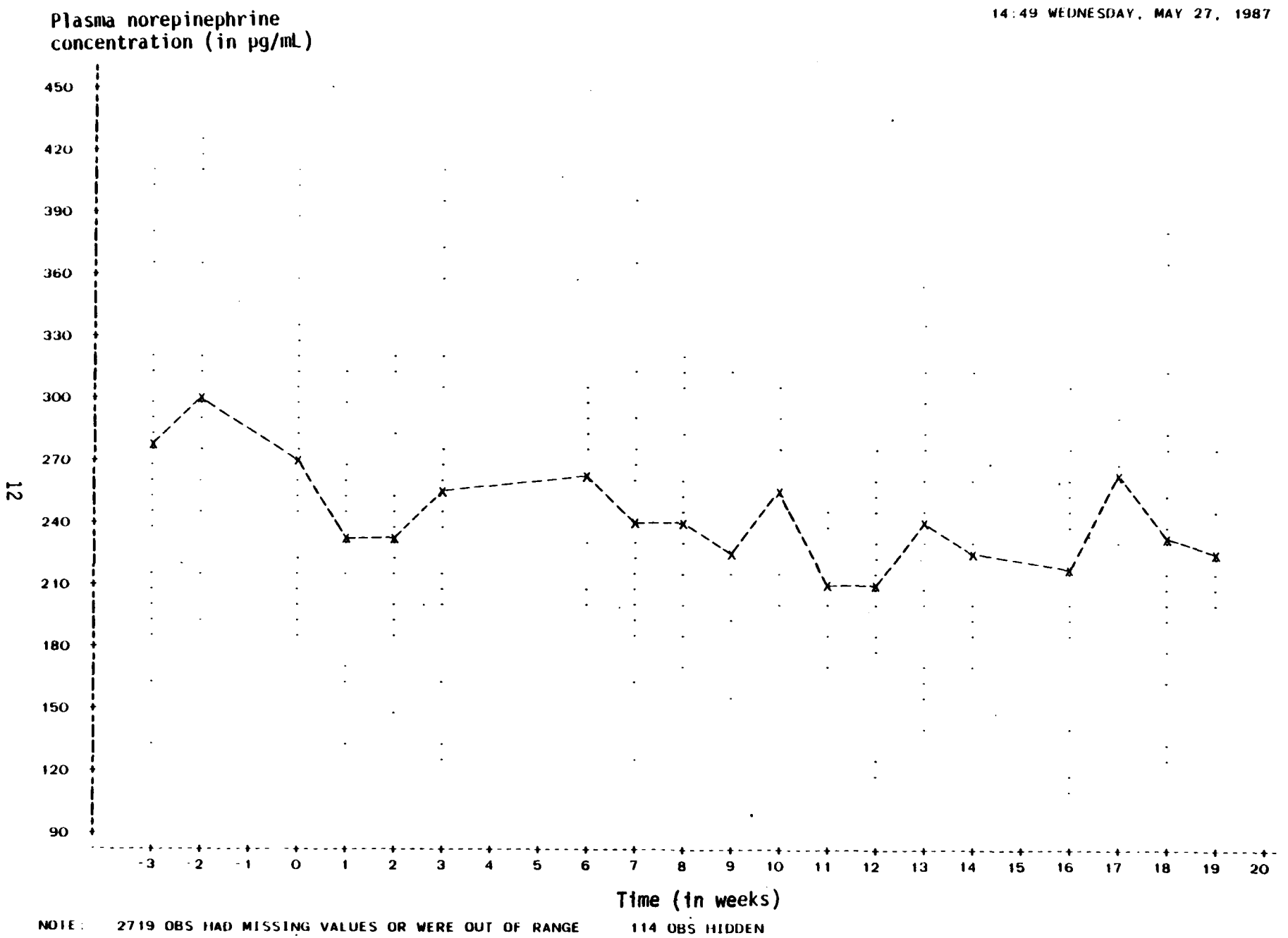

Figure 4. Norepinephrine concentration data scatter diagram (sham-exposure group).

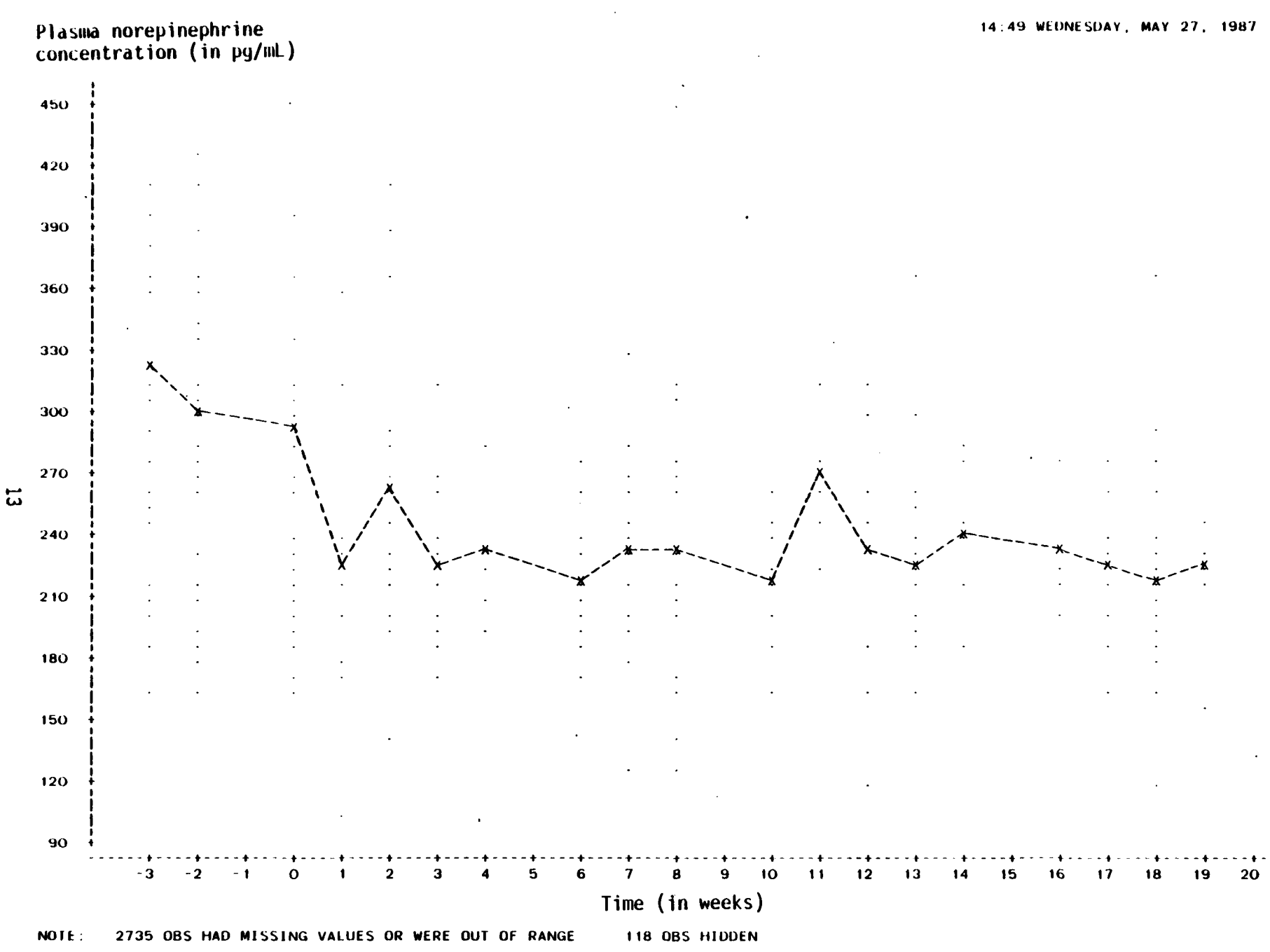

Figure 5. Norepinephrine concentration data scatter diagram (exposure group).

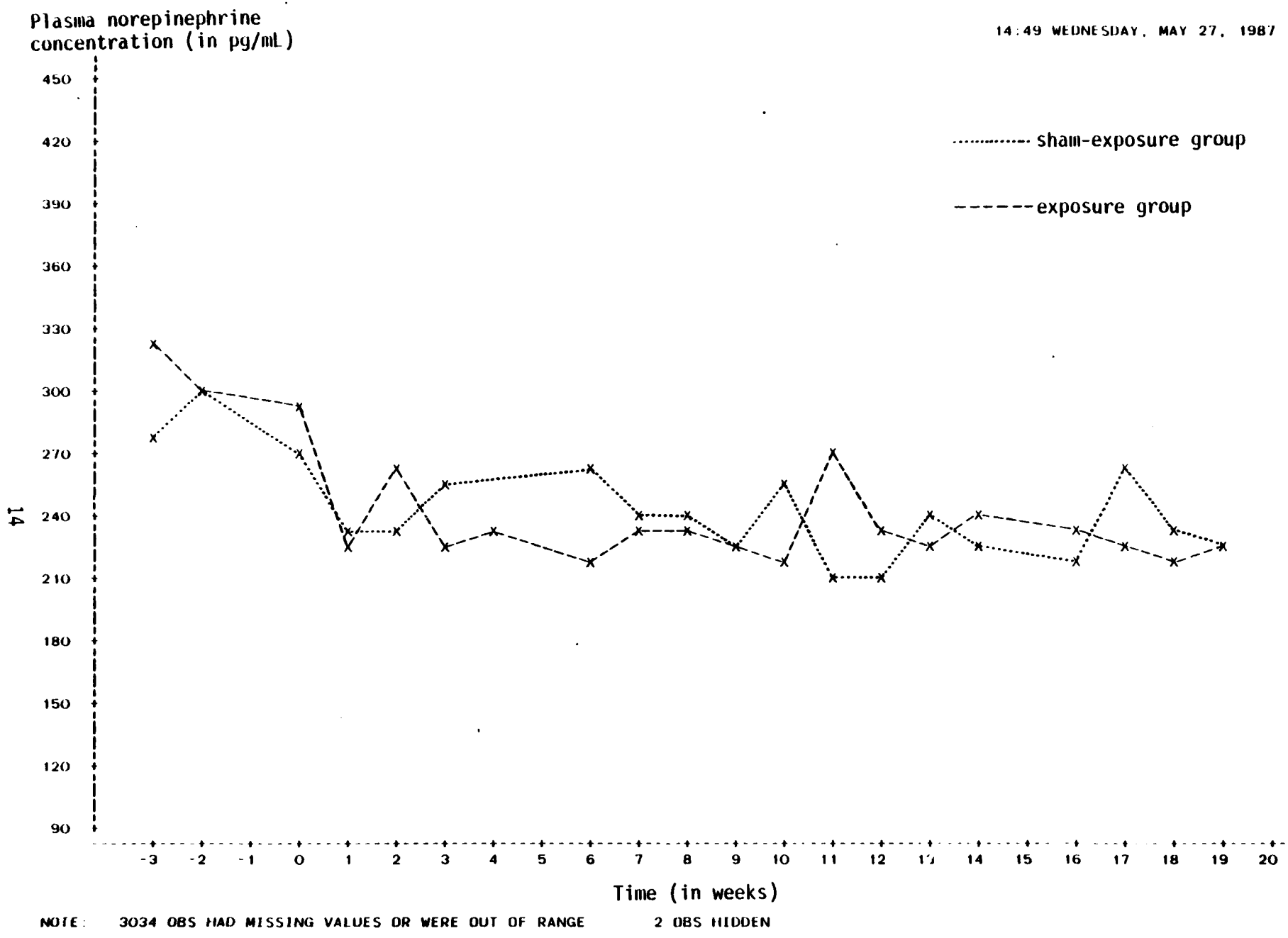

Figure 6. Mean plasma norepinephrine concentrations versus time.

significance in describing the collected data. Various diagnostic procedures, including model lack-of-fit tests, residual analysis, and autoregressive analysis, were then applied to the model to check its validity. Appendix B contains a detailed description of this statistical methodology, as well as the individual analyses for each of the three catecholamines.

The statistical analysis indicated that there was no significant difference between the sham-exposure and exposure groups. The final polynomial model was solely a function of time. Resting norepinephrine levels were at their highest value (approximately 299 pg/mL, as calculated from the model derived in the norepinephrine statistical analysis of Appendix B) at the study onset (week -3). The resting level then gradually declined, reaching its lowest point of an estimated 222 pg/mL at week 13 of the study. Norepinephrine concentration then appeared to rise, reaching a value of about 232 pg/mL at week 19 of the study, which was the last week for which data was available. Since no data were taken beyond week 19, there was no effort to extrapolate a value for week 29 of the study.

Further analysis determined the smallest change in resting norepinephrine concentration (between exposure and sham-exposure groups) that the protocol was capable of detecting. If there were any RFR-induced effects on the resting concentration of norepinephrine, they would have to lie within the range of $\pm$ 15 pg/mL from the estimated resting concentration of 273 pg/mL. Since values of norepinephrine between 258 pg/mL and 288 pg/mL are considered normal in unstressed rats, there was no indication that chronic RFR exposure resulted in any stress to the animals, as measured by plasma norepinephrine.

Plasma epinephrine. Appendix G contains the data collected during the pre-radiation and radiation periods for both exposure and sham-exposure groups. Like norepinephrine, this hormone also displayed a variance about the established resting level due to varying amounts of animal activity. Since plasma epinephrine concentrations were sensitive to handling and related stresses, each animal was given 30 min to allow the epinephrine concentration to return to the basal value.

Figures 7 and 8 present the raw epinephrine concentration data in scatter diagram form (the dotted lines pass through the mean epinephrine response at each week data were collected). Once again, the mean epinephrine values in both exposure and sham-exposure groups declined in the initial 3 weeks of the study. This decline was attributed to the animals being inadequately preconditioned to

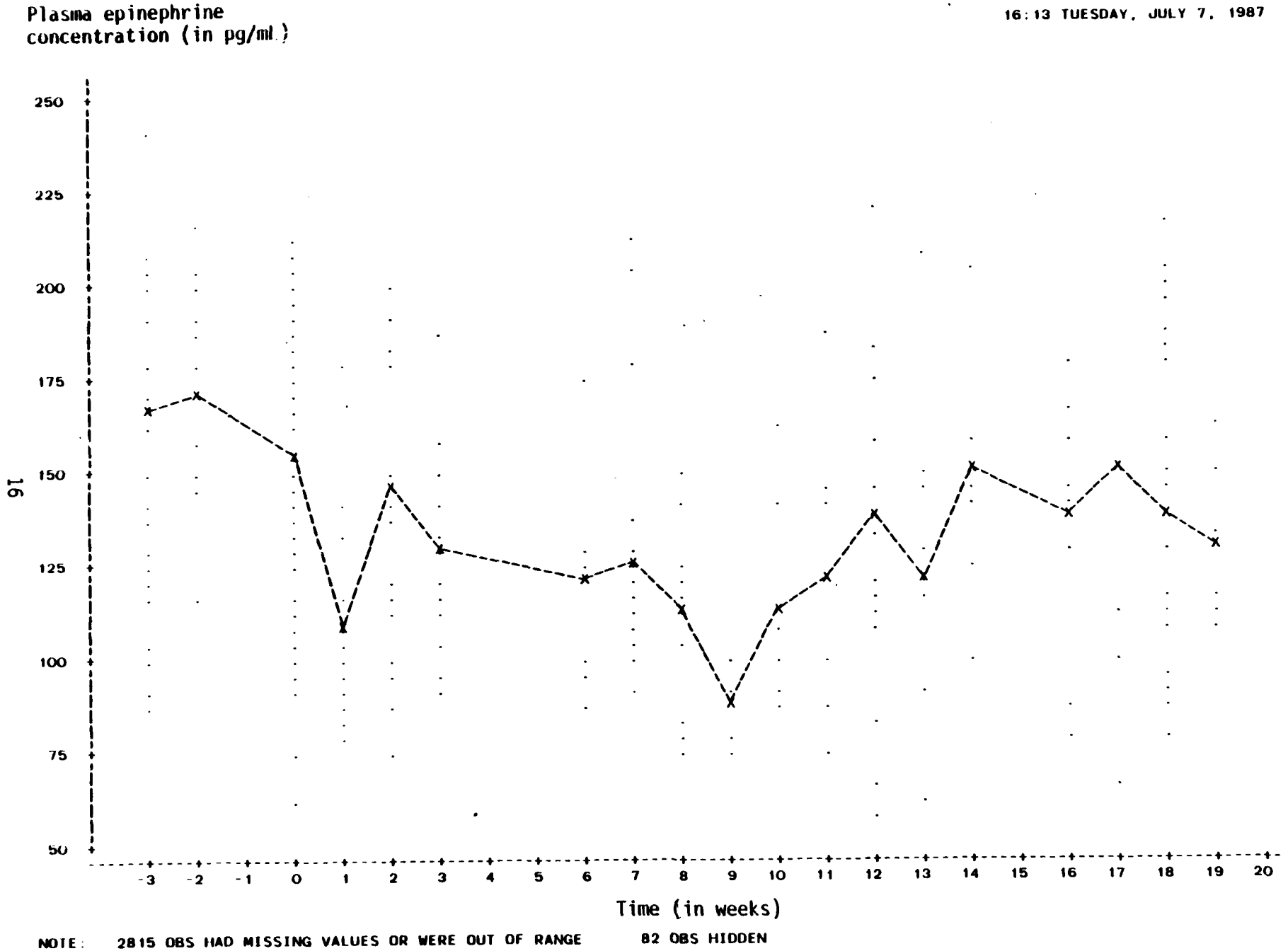

Figure 7. Epinephrine concentration data scatter diagram (sham-exposure group).

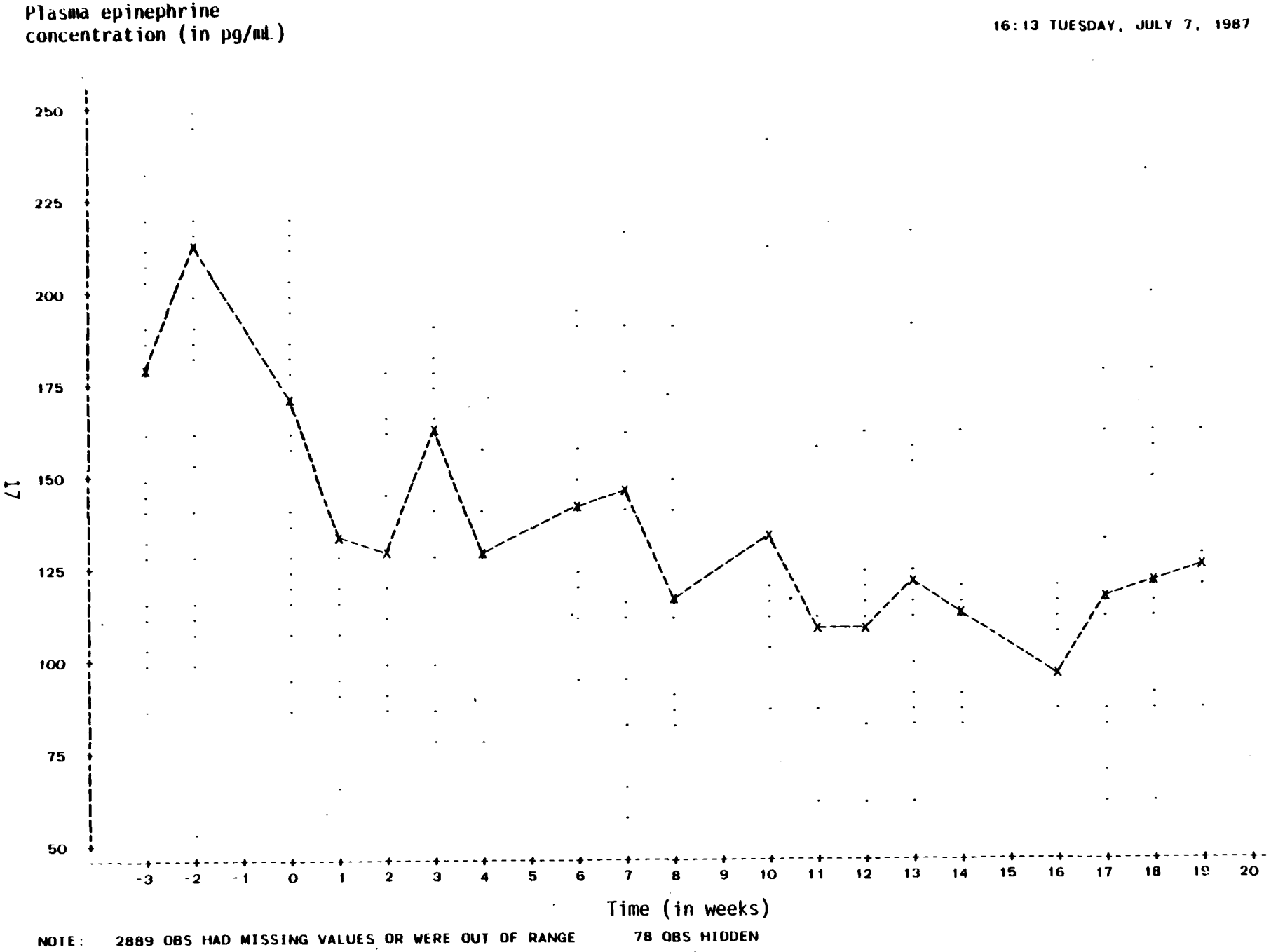

Figure 8. Epinephrine concentration data scatter diagram (exposure group).

the sampling boxes. Once the animals adapted to the sampling box environment, the epinephrine concentrations in both RFR-exposed and sham-exposed animals remained about the same. The small amount of "spikiness" in the plots was the random effect of sampling within a population.

The mean epinephrine concentrations in the exposure and sham-exposure groups did not seem to be significantly different when the two plots were compared to one another (Fig. 9). This evidence suggested tnat chronic exposure to 435-MHz RFR did not affect the resting concentrations of plasma epinephrine. A statistical analysis was then performed on the epinephrine data to test this hypothesis.

The statistical analysis involved building a polynomial function relating epinephrine concentration, time, and RFR radiation in the same manner as the previous hormones (ACTH, corticosterone, prolactin, and norepinephrine). The terms of the polynomial model were then tested to determine their significance in describing the epinephrine data set. The final model, which was independent of RFR, was then verified using lack-of-fit, residual analysis, anc autoregression techniques. The complete statistical analysis is included in Appendix B.

The analysis concluded that RFR had no effect on the exposure group when compared to the sham-exposure group. Epinephrine concentration during the study did display a time dependence, however, decreasing from an estimated initial concentration of 181 pg/mL at the study onset (week -3) to a low of 119 pg/mL during the exposures (week 12), and then increasing to about 134 pg/mL at week 19, the last week for which data were available. Once again, no effort was made to use the epinephrine model as a forecasting tool for week 29. Further analysis indicated that, if there were any RFR-induced effects, they had to lie within a range of $\pm$ 13 pg/mL from the resting value of 159 pg/mL. Since resting epinephrine concentrations between 146 pg/mL and 172 pg/mL are considered normal in unstressed rats, there was no indication that long-term RFR exposure produced any stress as measured by plasma epinephrine concentrations.

Plasma dopamine. Appendix L contains the data collected during the pre-radiation and radiation periods for both exposure and sham-exposure animals. The variance in the data, as mentioned before, derived principally from various levels of animal activity immediately before sampling. The 30-min acclimation time allowed dopamine concentrations to return to the resting, basal level.

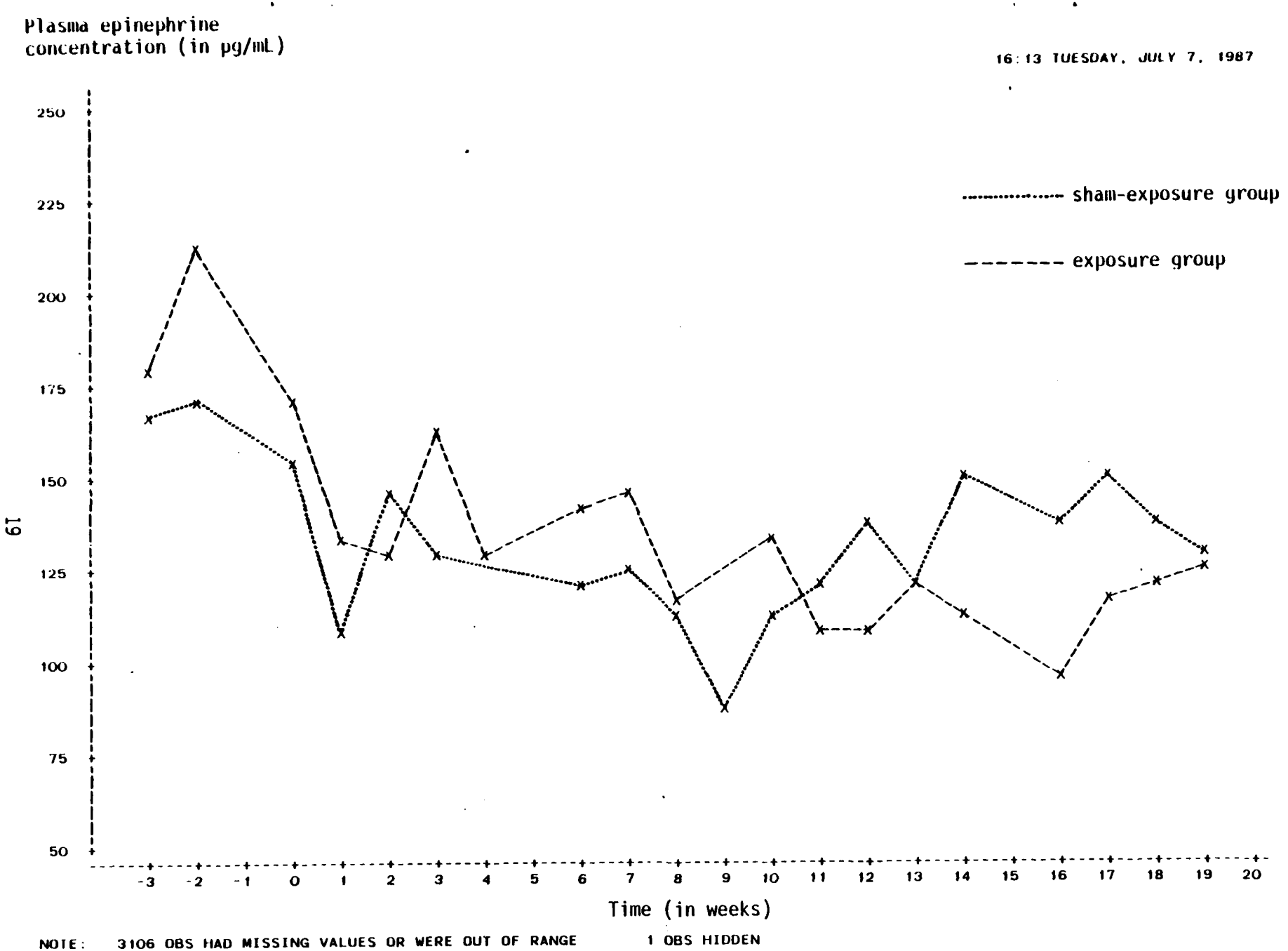

Figure 9. Mean plasma epinephrine concentrations versus time.

Figures 10 and 11 present the raw dopamine concentration data in scatter diagram form (the dotted lines pass through the mean dopamine response at each week data were collected). Again, the mean dopamine response in both exposure and sham-exposure groups declined in the initial 3 weeks of the study. This decline was similar to the observations noted in the other hormones assayed (ACTH, corticosterone, prolactin, norepinephrine, and epinephrine) and was attributed to the same source (animals inadequately preconditioned to sampling box). After the animals adapted to the sampling box environment, the dopamine values in both exposure and sham-exposure groups tended to stabilize (weeks 1 through 19). The spikiness in the plots was a result of random sampling within both populations.

Mean plasma dopamine concentrations did not appear to be larger in the exposure group when compared to the sham-exposure group (Fig. 12). If anything, the opposite seemed to be the case for the length of the experiment. This result indicated that chronic exposure to 435-MHz RFR did not induce physiological changes in the rat population that were manifested as increased resting dopamine concentrations. A statistical analysis was therefore performed on the data set to test this hypothesis.

The statistical analysis performed was identical in procedure to that used in the analysis of the other study hormones. A detailed description of the general methodology, and the specific dopamine analysis, is given in Appendix B. The analysis for all hormones used the SAS Statistical Software resident on the Georgia Tech IBM 4381 mainframe to run tests and produce the analysis hardcopy.

The analysis gave no indication of increased plasma dopamine in the exposure group when compared to the sham-exposure group. In fact, the estimated dopamine concentration in the exposure group remained significantly smaller than that of the sham-exposure group from the initiation of exposures to the termination of the experiment. Resting dopamine values were at their highest for week -3 of the study (about 62 pg/mL sham-exposed, 65 pg/mL exposed). The resting levels of both groups then declined, reaching the lowest value of 32 pg/mL at week 12 (sham-exposed); 20 pg/mL at week 16 (exposed). Beyond these points, dopamine concentration gradually increased, with estimated concentrations of 39 pg/mL (sham-exposed) and 21 pg/mL (exposed) at week 19, the last week for which data were collected.

Further analysis showed that the smallest change in resting dopamine concentration that the protocol could reliably detect was about 6 pg/mL above or

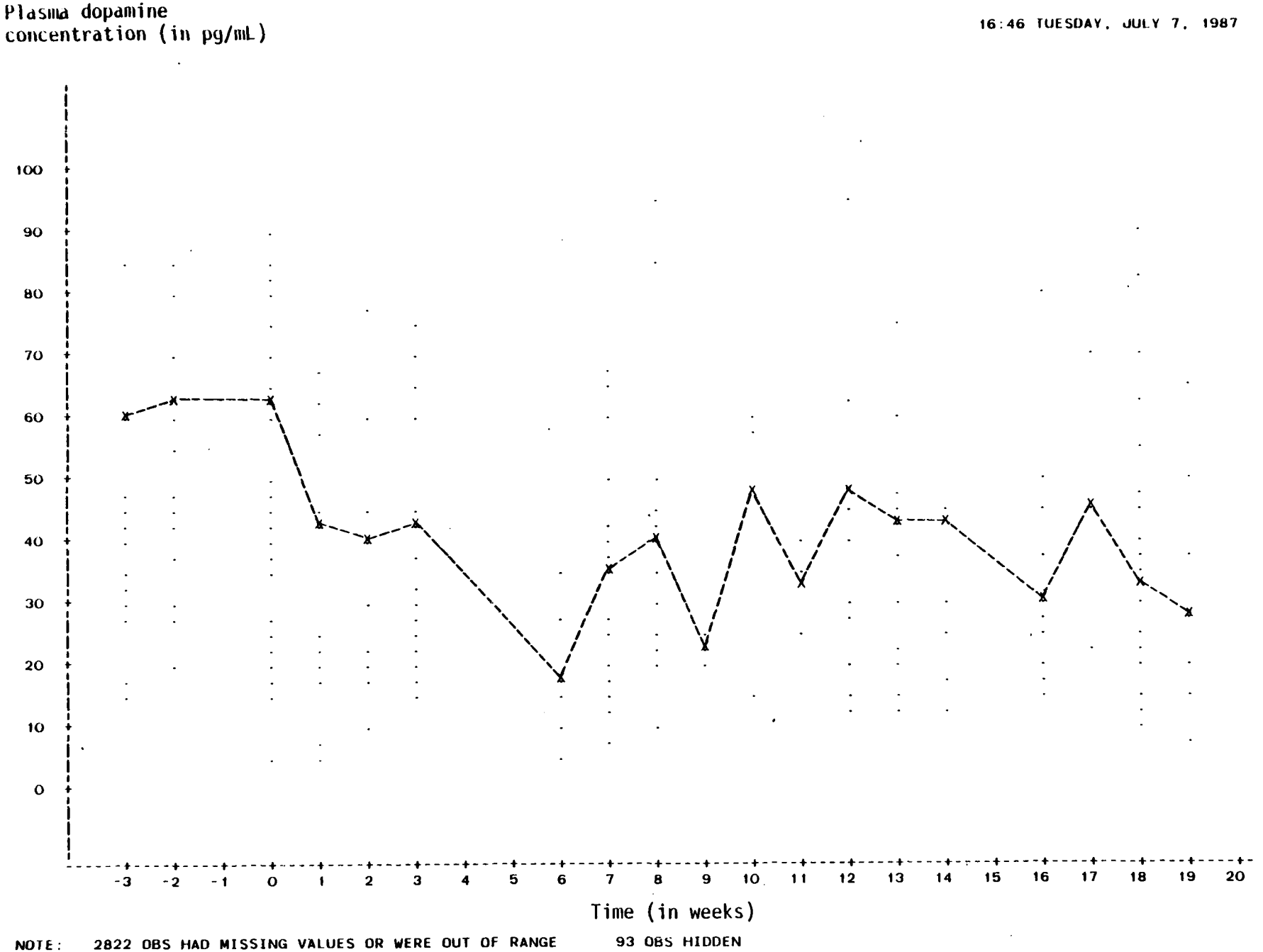

Figure 10. Dopamine concentration data scatter diagram (sham-exposure group).

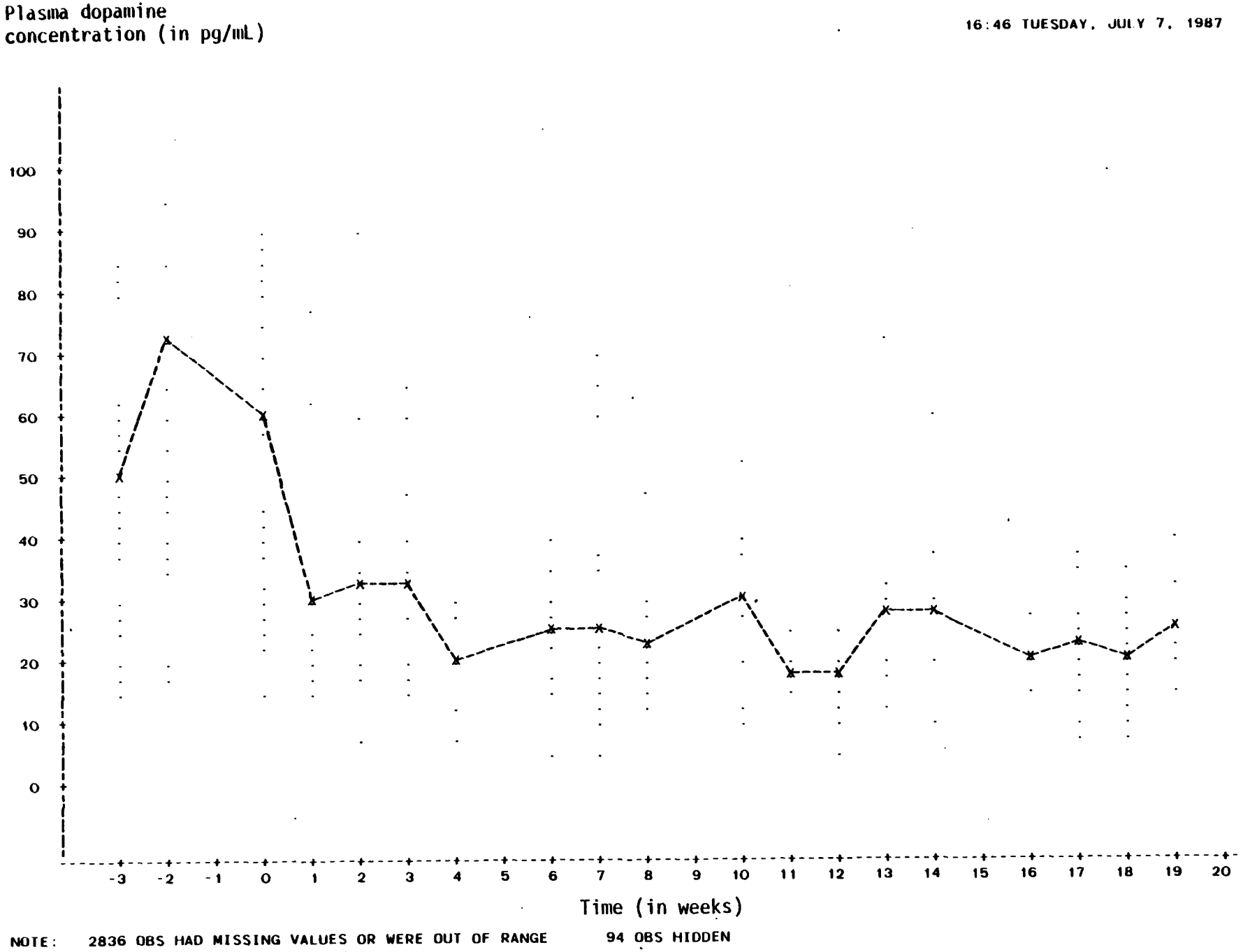

Figure 11. Dopamine concentration data scatter diagram (exposure group).

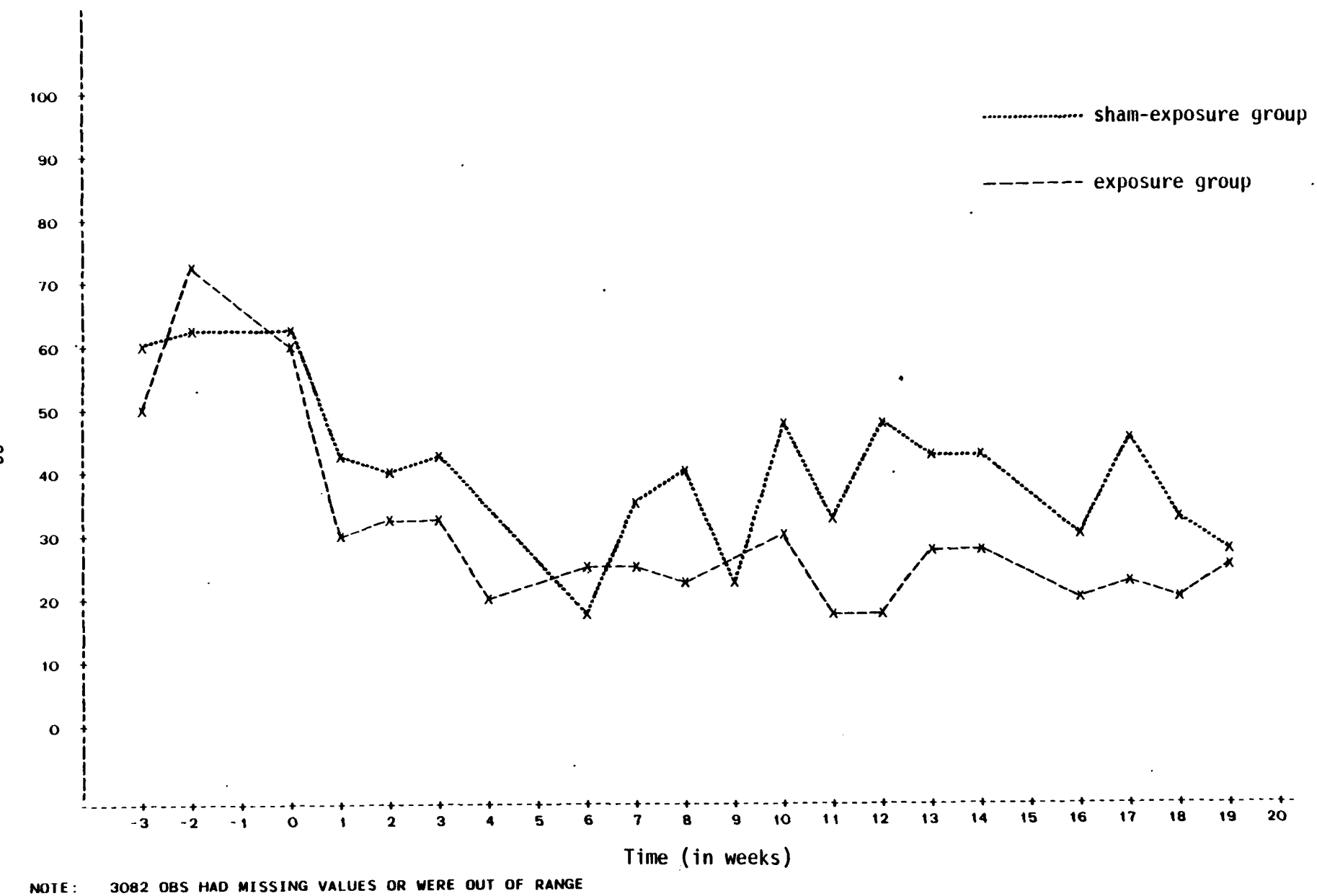

Figure 12. Mean plasma dopamine concentrations versus time.

below an estimated resting concentration of 51 pg/mL. This analysis indicated that, if RFR increased resting dopamine levels above 57 pg/mL, the protocol would have found a significant positive RFR effect. In fact, dopamine concentrations of up to 120 pg/mL were considered normal for a population of healthy, unstressed Sprague-Dawley rats. Therefore, there was no indication that chronic exposure to low-level 435-MHz RFR produced any stress in the exposure group (when compared to the sham-exposure group) as measured by the concentration of blood-borne dopamine.

IV. DISCUSSION

Minute amounts of free (unconjugated) catecholamines are normally found in both human and animal blood plasma. These hormones undergo rapid changes which reflect sympathetic nerve activity [18,19]. The radioenzymatic techniques available for quantitative determinations of norepinephrine, epinephrine, and dopamine in a few microliters of plasma permit monitoring of the sympathoadrenal activity in small laboratory animals such as the rat.

Arterial blood pressure, ambient temperature, body temperature, physiological activity, and certain biological characteristics (e.g., animal strain) have an effect on the level of circulating plasma catecholamine concentrations [20]. Different strains of rats have dissimilar levels of resting catecholamines [21,22]. Both normotensive and hypertensive rats show the same catecholamine response at rest, but hypertensive rats show a greater catecholamine response during stress [21,23].

For a particular strain of animal, the resting level of plasma catecholamines is always the same [24], permitting measurement of increases in plasma catecholamine concentration and (from these increases) evaluation of the level of stress an animal underwent [25,26]. The stronger a stress and the longer its duration, the higher the concentration of plasma epinephrine, norepinephrine, and in some cases dopamine [27]. Even a small reduction of blood volume increases plasma catecholamine levels [28,29].

To obtain reliable measurements of circulating catecholamines in rats required appropriate methods for blood collection to avoid catecholamine increase due to physical stress [16]. In this study, resting levels of catecholamines were considerably lower in rats whose blood samples were collected from indwelling cannulas than values where blood was obtained by decapitation or other stressful methods.

The results of our experiment indicate that exposure to chronic low-level RFR did not represent a stress measurable as an increase in norepinephrine and epinephrine concentration of irradiated rats. Similar results were obtained when plasma ACTH, plasma corticosterone, and plasma prolactin were determined in identical situations [2,3].

In this study, plasma dopamine decreased in RFR-exposed animals. Though significant, the small plasma dopamine decrease might not be physiologically important. It would be of interest to ascertain whether this lowered dopamine

concentration persists after RFR exposure is interrupted for several days or weeks (the rats were removed from the RFR field for 30 min to obtain the blood samples). The large individual variation observed in the plasma catecholamine levels of both RFR-exposed and sham-exposed animals was probably the consequence of various levels of animal physiological activity during or just before blood sampling. It is known, for instance, that during sleep plasma levels of norepinephrine and epinephrine are below those of the resting state [30].

Although plasma catecholamine half-life is only 1 to 3 min [15], a strong stimulus leaves plasma catecholamine levels relatively high for 10 to 15 min. For this reason, blood was sampled from the resting animals 30 min after gentle placement in the sampling boxes, permitting plasma catecholamine levels to return to the resting level.

During the 6-month study duration, the rats aged somewhat. Some investigators have reported changes in catecholamine secretion induced by aging [31,32,33]. However, new studies demonstrate that aging does not change the rat's responsiveness to either internal or external stimuli that evoke catecholamine secretion [34]. The same study failed to find changes over a several month period in resting plasma catecholamine concentration of rats.

In conclusion, our results indicated that a 435-MHz pulsed-wave environment did not increase resting plasma catecholamine concentrations in rats. The statistical analysis of the data indicated that if there were any RFR-induced effects on resting plasma catecholamine concentrations, they would lay within a range of $\pm$ 15 pg/mL from an estimated resting concentration of 273 pg/mL in norepinephrine; $\pm$ 13 pg/mL from an estimated resting concentration of 159 pg/mL in epinephrine; and $\pm$ 6 pg/mL from an estimated resting concentration of 51 pg/mL in dopamine. These values are not typical of rats exposed to stress. Therefore, this study concludes that a 1.0 mW/cm^2 435-MHz pulsed-wave (1.0 μs pulse width, 1 kHz pulse rate) RFR environment did not induce any detectable increase in stress, as measured by resting catecholamine concentrations in the exposure group of cannulated male Sprague-Dawley rats when compared to the sham-exposure group.

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APPENDIX A

RAW NOREPINEPHRINE DATA SPREADSHEETS

NCRE (pg/ml) Control I

Rat #	Group	-3WK	-2WK	-1WK	TIME 1WK	2WK	3WK	4WK	5WK	6WK	7WK	8WK	9WK	10WK	11WK	12WK	13WK	14WK	15WK	16WK	17WK	18WK	19WK	20WK	21WK	22WK	23WK	24WK	+2	+5
1		245	220	229						207				219						200										
2		279	247	255						206				201						186										
3		210	190	220						233				199						194										
4		300	294	317						290				280						217										
5		285	320	260						281				310						310										
6		280	317	235						303				305						288										
7		46	463	270						282				—						120										
8		320	327	291						307				290						146										
9		318	310		-	½					290						261					180								
10		266	223	190	½						198						—					—								
11		240	203	255							204						245					—								
12		200	—	225							219						230					209								
13		190	156	218							216						203					213								

NCRE (pg/ml) Controls II

Rat #	Group	-3WK	-2WK	-1WK	TIME 1WK	2WK	3WK	4WK	5WK	6WK	7WK	8WK	9WK	10WK	11WK	12WK	13WK	14WK	15WK	16WK	17WK	18WK	19WK	20WK	21WK	22WK	23WK	24WK	+2	+5
14		268	314		224						211						247					217								
15		280	261		241						210						189					231								
16		293	312		255						266						131					207								
17		221	210		231						218						209					232								
18		293	308		237						225						217					241								
19		212	189		235						218						245					180								
20		256	227		218						228						260					197								
21		—	191		240						232						230					240								
22		164	—			247								221					261				235							
23		132	190			240								317					205				205							
24		264	252			212								161					—				—							
25		260	261			264								218					269				219							
26		271	220			218								198					231				207							

NORE (pg/ml) Control III

Rat #	Group	-3WK	-2WK	0WK	TIME 1WK	2WK	3WK	4WK	5WK	6WK	7WK	8WK	9WK	10WK	11WK	12WK	13WK	14WK	15WK	16WK	17WK	18WK	19WK	20WK	21WK	22WK	23WK	24WK	+2	+3
27		380	299			207					202							170					226							
28		245	207			-					312							314					-							
29		263	260			311					371							186					250							
30		267	218			307					268							174					-							
31		318	294			373					186							193					205							
32		305	360			-					126						265						131							
33		190	216			270					185						-						205							
34		280	210	163							251						276						194							
35			430	301	138						260						171						364							
36			410	-	170						-						302						198							
37			370	290	-						205						159						318							
38			320	274	265						256						-						136							
39			195	207	250						283						208						207							

NORE (pg/ml) Control IV

Rat #	Group	-3WK	-2WK	0WK	TIME 1WK	2WK	3WK	4WK	5WK	6WK	7WK	8WK	9WK	10WK	11WK	12WK	13WK	14WK	15WK	16WK	17WK	18WK	19WK	20WK	21WK	22WK	23WK	24WK	+2	+3
40		318	294		196						291				171					206										
41		-	218		219						226				-					258										
42		380	316		-						234				199					266										
43		296	415		314						314				248					-										
44		315	-		149						166				-					244										
45		-	336		188						-				190					116										
46			418	-	326						192				240					243										
47			196	315	288						400				-					245										
48			-	286		276						306				222							-							
49			316	290		401						264				118							136							
50			316	246		414						221				180							168							
51			-	-		213						214				-							286							
52			30	248		206						-				208							368							

NORE (pg/ml) Control V

Rat #	Group	-3WK	-2WK	0WK	TIME 1WK	2WK	3WK	4WK	5WK	6WK	7WK	8WK	9WK	10WK	11WK	12WK	13WK	14WK	15WK	16WK	17WK	18WK	19WK	20WK	21WK	22WK	23WK	24WK	+2	+5
53		-		342		202					204						213					278								
54		412		390		325					317						249					229								
55		186		-		361					204						257					207								
56		216		-		164					-						235					317								
57		291		219		125					325						164					381								
58		-		269		250					171						139					254								
59		-	280			135					232						300					-								
60		198	245			168					-						315					168								
61		318	263		249						187					256						268								
62		318	299		241						235					281						231								
63		402	315		202						218					254						290								
64																														

NORE (pg/ml) MWI

Rat #	Group	-3WK	-2WK	0WK	TIME 1WK	2WK	3WK	4WK	5WK	6WK	7WK	8WK	9WK	10WK	11WK	12WK	13WK	14WK	15WK	16WK	17WK	18WK	19WK	20WK	21WK	22WK	23WK	24WK	+2	+5
1		392		232	220					226				217								266								
2		307		270	360					266				205								241								
3		-		230	217					217				201								218								
4		264		241	205					203				193								195								
5		195		190	177					176				185								162								
6		-		194	207					192				224								191								
7		370		225	214					277				245								231								
8		231		190	242					203				261								224								
9			192	193	235						235						255						244								
10			274	-	235						-						190						-								
11			217	334	-						-						197						241								
12			246	-	-						197						195						224								
13			377	266	198						198						227						225								

NORE (pg/ml) MW II

Rat #	Group	-3WK	-2WK	3WK	TIME 1WK	2WK	3WK	4WK	5WK	6WK	7WK	8WK	9WK	10WK	11WK	12WK	13WK	14WK	15WK	16WK	17WK	18WK	19WK	20WK	21WK	22WK	23WK	24WK	+2	+5
14		380	246		296 →					-				246							223									
15		266	-		219 →					241				-							206									
16		261	265		245 →					218				237							217									
17		-	342		-	-				207				261							164									
18		-	300		227 →					194				217							166									
19		164	258		220 →					185				219							227									
20		191	264		277 →					234				228							242									
21		261	220		271 →					242				164							261									
22		298	188			271					205							181				217								
23		316	217			257					202							241				205								
24		264	281			244					268							-				266								
25		203	164			220					201							215				180								
26		255	184			221					217							218				180								

NORE (pg/ml) MW III

Rat #	Group	-3WK	-2WK	3WK	TIME 1WK	2WK	3WK	4WK	5WK	6WK	7WK	8WK	9WK	10WK	11WK	12WK	13WK	14WK	15WK	16WK	17WK	18WK	19WK	20WK	21WK	22WK	23WK	24WK	+2	+5
27		264	-			284					260							216				216								
28		316	305			292					-							246				246								
29		416	505			416					271							286				158								
30		564	311			270					235							-				216								
31		124	216			216					214							279				230								
32		255	-			-					215							-				-								
33		215	305		208						270							185				189								
34		-	695		206						265							225				225								
35			-	346	-						266							-				-								
36			425	-	187						-							270				320								
37			202	186	216						170							168				168								
38			186	307	242						168							227				277								
39			216	-	229						125							165				165								

NORE (pg/ml) MW IV

Rat #	Group	-1WK	-2WK	0WK	TIME 1WK	2WK	3WK	4WK	5WK	6WK	7WK	8WK	9WK	10WK	11WK	12WK	13WK	14WK	15WK	16WK	17WK	18WK	19WK	20WK	21WK	22WK	23WK	24WK	+2	+5
40		219	57[illegible]		230						181				259						277									
41		214	265		42[illegible]						30[illegible]				2[illegible]						-									
42		211	191		-						126				25[illegible]						22[illegible]									
43		-	174		378						277				-						279									
141		418	2[illegible]		216						227				-						-									
45		2[illegible]	216		209						-				239						248									
46			- 287		-						283				318						-									
47			315	316		171					276					301						266								
48			412	-		236					192					120						203								
49			395	398		238					-					265						188								
50			218	286		-					447					275						120								
51			286	167		187					218					-						264								
52			441	202		454					203					-						291								

NORE (pg/ml) MW V

Rat #	Group	-1WK	-2WK	0WK	TIME 1WK	2WK	3WK	4WK	5WK	6WK	7WK	8WK	9WK	10WK	11WK	12WK	13WK	14WK	15WK	16WK	17WK	18WK	19WK	20WK	21WK	22WK	23WK	24WK	+2	+5
53		313		210			219					212					218					-								
54		365		282			-					214					265					191								
55		345		215			261					306					241					195								
56		480		2[illegible]			265					235					196					228								
57		[illegible]		400			188					206					257					241								
58		315		422			216					-					301					265								
59		612		640			-					262					68					230								
60		415		474				222				312					312					285								
61		412		269				282			246						264					265								
62		2[illegible]		241				210			240						159					221								
63		261		201				158			246						250					196								

APPENDIX B

STATISTICAL METHODOLOGY

APPENDIX B

STATISTICAL METHODOLOGY

The balanced design of this experiment (requiring that 25 animals from each 100 animal group be sampled once every 3 weeks for stress hormones) should have produced data easily tested by balanced, 2-way analysis of variance (ANOVA) statistics with 12 levels of factor A (time) and 2 levels of factor B (RF radiation). However, data collection did not proceed according to protocol in that, in numerous cases, samples were collected at odd intervals (invalidating the orthogonality of the design) and the number of samples taken per week varied above and below the 25 animal mark (unbalancing the design). These two factors combined to lower the power of ANOVA statistics (power being defined as the ability to reject the null hypothesis given the null hypothesis should be rejected) trying to test the model

$$y_{ijk} = \mu + \tau_i + \beta_j + \tau\beta_{ij} + \varepsilon_{ijk}, \qquad \text{(B-1)}$$

where y_{ijk} = hormone concentration (response),

μ = the normal hormone resting concentration,

τ_i = the change in hormone resting concentration induced by RFR,

β_j = the change in hormone resting concentration induced by time,

$\tau\beta_{ij}$ = the change in hormone resting concentration induced by the interaction between RFR and time, and

ε_{ijk} = noise within the system (sampling and assaying errors)

for the following hypotheses:

H_0: $\tau_0 = \tau_1 = 0$,
H_1: τ_0 or $\tau_1 \neq 0$ (RFR-induced effects), (B-2)

H_0: $\beta_1 = \beta_2 = \ldots = \beta_{12} = 0$.
H_1: at least one $\beta_j \neq 0$ (time-induced effects), (B-3)

H_0: $\tau\beta_{ij} = 0$, and
H_1: at least one $\tau\beta_{ij} \neq 0$ (interaction between RFR and time). (B-4)

However, examination of the collected data suggested an alternative approach in that the data resembled what might have been collected in an unplanned experiment monitoring over time the operation (in this case, characterized by resting animal hormone concentrations) of an established RF radiation facility. Data of this type are often successfully treated by employing linear regression techniques to develop, build, and test a linear (or intrinsically linear) model whose parameters can be used to predict the system response at various treatment levels. Therefore, we decided to proceed with a regression approach to data analysis.

Plasma Norepinephrine Statistical Analysis.

Examination of the norepinephrine scatter diagrams of Figures 4 and 5 yield an essentially linear norepinephrine response versus time beyond week 0 of the study. There was, however, a certain amount of positive curvature present at both the study initiation and study conclusion, particularly in the sham-exposure group. Therefore, a quadratic polynomial function was empirically chosen to test for RFR effects within the exposure and sham-exposure groups. Thus, the norepinephrine response was modelled with a nonzero intercept β_0 and an RFR-induced effect on this intercept ($\alpha_0 z$), a nonzero linear slope β_1 and an RFR-induced effect on this slope ($\alpha_1 z$), and a quadratic coefficient β_{11} and RFR-induced effect on this curvature ($\alpha_{11} z$). The statistical significance of these terms determined the importance of their contribution to the final model. The equation describing the initial model was therefore:

$$y = \beta_0 + \beta_1 x + \beta_{11} x^2 + \alpha_0 z + \alpha_1 zx + \alpha_{11} zx^2 \qquad \text{(B-5)}$$

where y = plasma norepinephrine concentration (in pg/mL),
x = time (in weeks), and
z = a categorical variable with value 0 for animals in sham-exposure group and value 1 for animals in exposure group.

Raw data from the norepinephrine spreadsheet (Appendix A) were put on computer file. A Statistical Analysis System (SAS) formatting program (Appendix C) was prepared to read the data and perform the desired statistical tests on the model.

The first test identified terms within the model which contributed the least toward forming a statistically significant regression. These procedures

were used in combination with an initial regression on the general model (not included) to evaluate the statistical significance of terms modelling the norepinephrine concentration time dependency and terms modelling the RFR-induced effects on norepinephrine concentration. Two types of model "building" procedures were used: forward stepwise regression and maximum R^2 regression. Forward stepwise regression produced a model by calculating F statistics for all variables not in the model, and then adding a variable to the model if its F statistic was significant at a given α risk (for this reason, the forward procedure begins with no variables in the model). Once a variable was added to the model, the procedure recalculated F statistics for all the terms in the model, and rejected any terms whose F statistic rose above a given α risk. In this manner, forward stepwise regression eventually settled on a model including all terms whose α risk was low enough to permit initial entry and then not be rejected upon the addition of other terms.

Maximum R^2 regression took this procedure further, producing lists of the best 1-parameter model, best 2-parameter model, best 3-parameter, etc., until all of the parameters were included in the final model. This procedure permitted discrimination of different models using number of parameters as a judgement criterion.

Both forward stepwise and maximum R^2 regressions indicated that the model which best fit the data was:

$$y = \beta_0 + \beta_1 x + \beta_{11} x^2, \qquad \text{(B-6)}$$

where

$\beta_0 = 272.8$,

$\beta_1 = -7.79$, and

$\beta_{11} = 0.30$.

The entry and exit α risk was 0.10. The outputs of both regression procedures are included in Appendix D. Note that the absence of α terms indicated that, at a 0.10 risk, there was no statistical difference in plasma norepinephrine concentrations between the exposure and sham-exposure group. The estimated resting concentration of plasma norepinephrine, 272.8 pg/mL (β_0), agreed well with established values cited in the literature (300 $\pm$ 40 pg/mL). This agreement was an indication of no systematic error within the sampling/assaying procedure.

Both exposure and sham-exposure groups did display a time dependency in norepinephrine concentration. Resting norepinephrine levels were at their highest value (about 298.9 pg/mL) at the study onset (week -3). The resting level then gradually declined, reaching its lowest point of 221.8 pg/mL at week 13 of the study. Norepinephrine concentration then seemed to rise, reaching a value of 232.0 pg/mL at week 19 of the study, which was the last week data were taken. All of the just mentioned values were well within the normal bounds of plasma norepinephrine concentration in healthy, unstressed rats. Therefore, it seemed that chronic exposure to 435-MHz RFR did not result in an increase in stress (as measured by the concentration of plasma norepinephrine) in the exposure group when compared to the sham-exposure group.

The just mentioned conclusions could only be accepted once the assumptions used to build the final model were verified. These assumptions included no model lack-of-fit, NID(0, σ^2) residual distribution (meaning residuals were normal and independently distributed with mean zero and variance σ^2), and no model multicollinearity.

Since multiple observations of norepinephrine concentration were taken for the weeks containing data, it was possible to perform a model lack-of-fit test on the regression. The lack-of-fit involved breaking the sum-of-squares error from the regression into two components: sum-of-squares pure error, representing the actual variation due to the sampling and assaying process and sum-of-squares lack-of-fit, representing the variation due to the difference between the mean value at one week when compared to the fitted value at the same week. A test statistic was then computed comparing the sum-of-squares lack-of-fit to the sum-of-squares pure error; sufficiently high values of the test statistic indicated model lack-of-fit.

Sum-of-squares error was obtained from the ANOVA table produced in the regression procedure output. Sum-of-squares pure error was obtained by analyzing the experiment from 2-way, fixed effects ANOVA viewpoint. The sum-of-squares lack-of-fit was then computed from the difference of sum-of-squares error minus sum-of-squares pure error. Calculations to compute the critical value F_0 are detailed in Appendix E.

Since the computed test statistic F_0 was smaller than the critical value, there was insignificant model lack-of-fit. This indicated that the quadratic function modelling norepinephrine concentration versus time was a good empirical description of the data set. Under no lack-of-fit conditions, the mean square

error and mean square pure error should both estimate the population variance σ^2. Indeed, MS_E = 4462.5 and MS_{pe} = 4443.1, producing estimated sample standard deviations of 66.80 pg/mL and 66.66 pg/mL. These standard deviations were somewhat larger than those listed in the literature (by the criterion that a normal range covers a distance of about 4σ, the standard deviation indicated by the literature is about 20 pg/mL). However, the given estimates of σ were inflated by the presence of potential outliers. Since the value of Cook's D was not considered extreme (all had Cook's Ds of between 0.01 and 0.04), the 4 possible outliers (corresponding to animal 130 (week -3), animal 159 (week -3), animal 159 (week -2), and animal 134 (week 0)) were not rejected from the data set. The high values of these observations (all above 600 pg/mL) did tend to raise the mean values at those weeks, and thus inflated the estimates of the standard deviation.

The next model verification step involved examining the residual and partial residual plots to confirm the least squares regression assumption that the model errors were NID(0,σ^2). This step would defend the use of F tests to determine the statistical significance of the parameters. Additionally, this step would validate the statistics which produced tables listing confidence intervals of the norepinephrine concentrations. A number of residual plots suggested themselves immediately: residuals versus time, residuals versus predicted value of norepinephrine concentration, residuals versus animal case number, studentized residuals versus the previous three, and partial residual plots corrected for the model terms β_0, β_1, and β_{11}. Examination of the residual plots yielded no discernible patterns in the distribution of the residuals. Thus, the residuals were normally distributed with mean 0 and variance σ^2. The residual plots are included in Appendix F.

Since the data from this study arose as a time series, there was a possibility that the residuals were in some part autocorrelated to prior observations. To determine the extent of this autocorrelation, an autoregressive model building procedure (PROC AUTOREG from the SAS ETS series) was used with lag times of 0, 1, 2, 3, and 4 weeks.

Results of the autoregression (not included in report) indicated a significant amount of correlation between data at one week to data at the previous week (lag-1 autocorrelation). The autoregression also detected a considerably smaller (although statistically significant) lag-2 autocorrelation. Lag-1 correlation indicated that the best predictor of any single observation

was the previous observation for that particular animal (rather than the value yielded by substituting the parameter estimates and week number into the derived norepinephrine model). If the study purpose were to determine a predictive model of norepinephrine behavior in the rats, then the just mentioned conclusion would have dire consequences with regards to the model obtained in Appendix D. However, the main reason regression was chosen to model this data was not to produce a precictive model of norepinephrine versus time, but rather to determine whether or not two blocked groups (exposure and sham-exposure) displayed any differences in norepinephrine behavior. For this purpose, non-independence in the residuals does not call into question the overall conclusions drawn from the model. To compensate for this deficiency, it would only be necessary to raise the α risk used in determining the norepinephrine model. Since β_0, β_1, and β_{11} were found to be significant at probabilities less than 0.0001, this alteration of significance had no practical effect on the final model determined in the analysis. The large number of observations taken essentially made this data set relatively insensitive to potential problems (such as lack-of-fit or nonindependence in the residuals).

To complete the analysis, diagnostics to check for model multicollinearity and correlation between the terms were used. Examination of the listed condition numbers and matrix eigenvalues (being provided under separate cover) detected no troublesome values. This review indicated that the model did not display a significant degree of multicollinearity. Similarly, examination of the correlation matrix showed that correlations between the estimated values of β were all within tolerable limits. The highest degree of correlation was between the x and the x^2 term, which often occurs when using a polynomial model in linear regression.

For future reference, and for the sake of completeness, tables listing animal case number, observations (if taken) at each week, predicted value of norepinephrine concentration, standardized error of prediction, 95% confidence intervals on the mean value of the norepinephrine concentration, and residuals were prepared, as were tables containing animal case number, regular and studentized residual values, a graphical display of student residual values, and influence statistics (such as Cook's D). These tables were used to detect both outliers and influential data points in the norepinephrine data set.

To arrive at a conservative estimate of the minimum change due to RFR in resting norepinephrine concentrations which this protocol was capable of

detecting, the value of the operating curve parameter ϕ_B corresponding to the RFR factor (B) discussed at the beginning of the statistical methodology was calculated. This parameter was given by

$$\phi^2_B = \frac{naD^2}{2b\sigma^2} \qquad \text{(B-7)}$$

where n = number of replications per cell = 40,

a = number of levels of factor A = 12,

b = number of levels of factor B = 2,

σ^2 = population variance, and

D^2 = detection threshold.

Substituting in values for a, b, n, and the MS_{pe} as an estimate of σ^2 provided an operating curve parameter of

$$\phi_B = 0.1643\ D. \qquad \text{(B-8)}$$

To obtain a value of ϕ from the operating curve, the type I risk α and type II risk β were set to 0.05 and 0.10, respectively. Then, the value Φ was read from the fixed effects ANOVA curve with $\nu_1 = 1$ and $\nu_2 = 936$. This value was

$$\Phi_B = 2.4 \qquad \text{(B-9)}$$

Note that the degrees of freedom for the numerator, ν_1, and the degrees of freedom for the denominator, ν_2, were calculated with the equation

$$\nu_1 = b-1, \text{ and} \qquad \text{(B-10)}$$

$$\nu_2 = ab(n-1). \qquad \text{(B-11)}$$

The detection level was therefore

$$D_B = 14.60 \text{ pg/mL}. \qquad \text{(B-12)}$$

Thus, this protocol was able to conservatively detect an increase in resting plasma norepinephrine concentrations of 14.60 pg/mL about 90% of the time.

Plasma Epinephrine Statistical Analysis.

In many ways, the epinephrine scatter diagrams of Figure 7 and 8 closely resembled the norepinephrine scatter diagrams. Therefore, epinephrine concentration was modelled in a similar manner to norepinephrine. The equation

$$y = \beta_0 + \beta_1 x + \beta_{11} x^2 + \alpha_0 z + \alpha_1 zx + \alpha_{11} zx^2 \qquad \text{(B-13)}$$

where y = plasma epinephrine concentration (in pg/mL)
x = time (in weeks), and
z = a categorical variable with value 0 for animals in the sham-exposure group and value 1 for animals in the exposure group,

was tested for the significance of the coefficients α_0, α_1, and α_{11}. These terms described the RFR-interaction with the resting epinephrine concentration.

Data from the epinephrine spreadsheets (Appendix G) were subsequently put into a new file and a second SAS formatting program (included in Appendix H) was prepared to analyze the data.

The model indicated by the forward stepwise and maximum R^2 regression procedures was

$$y = \beta_0 + \beta_1 x + \beta_{11} x^2, \qquad \text{(B-14)}$$

where $\beta_0 = 158.80$,
$\beta_1 = -6.62$, and
$\beta_{11} = 0.28$,

with the x, y, and z variables as defined previously. The entry and exit risk were both set to 0.095. The outputs of both regression procedures are included in Appendix I. Note that the absence of α terms indicated that, at a risk of 0.095, there was no statistical difference in plasma epinephrine concentrations between the exposure and sham-exposure groups. The estimated resting concentration of plasma epinephrine, 158.8 pg/mL, also agreed well with established values cited in the literature (180 $\pm$ 35 pg/mL). This agreement was a further indication of no systematic error within the sampling/assaying procedure.

Epinephrine concentration in the sham-exposure and exposure groups displayed the same type of time dependency found in the norepinephrine concentrations. Since epinephrine and norepinephrine release within the body

are physiologically coupled, this was not a surprising find. Specifically, resting epinephrine values were at their highest value of 181.3 pg/mL at the study onset (week -3). The resting level then gradually declined, reaching its lowest point of 119.4 pg/mL at week 12 of the study. Epinephrine concentration slowly rose beyond that point to a value of 133.9 pg/mL at week 19, the last week for which data were taken. All of the just mentioned values are typical of resting epinephrine concentrations in normal, unstressed rats. It did not appear, therefore, that chronic exposure to 435-MHz RFR induced any stress, as measured by the resting concentration of plasma epinephrine, in the exposure group when compared to the sham-exposure group.

The just mentioned conclusions could only be accepted upon verification of the assumptions used in building the model. These assumptions included no model lack-of-fit, NID(0,σ^2) residual distribution, and no model multicollinearity.

First, the model was checked for lack-of-fit (Appendix J). The mean square error and mean square pure error were 3359.31 and 3296.69 respectively, yielding sample standard deviation estimates of 57.96 pg/mL and 57.42 pg/mL. Since both of these estimates were rather close to one another, lack-of-fit was probably not significant. The computed lack-of-fit test statistic was then found to be smaller than the critical value. This test confirmed that model lack-of-fit was not present.

The epinephrine data set was then checked for outlier data values before generating residual plots. Three observations at week -3 (animal #53, [epinephrine] = 560 pg/mL; animal #57, [epinephrine] = 806 pg/mL; and animal #62, [epinephrine] = 540 pg/mL) were determined to be outliers and were subsequently removed from the data set. All three points had values of Cook's D greater than 0.05, and thus were overly influential in comparison with other data points from week -3. Once the data set was edited, residual plots were generated to check the assumption that the model errors were distributed NID(0, σ^2). Appendix K contains the epinephrine residual plots. Examination of the plots yielded no obvious patterns or problems, thereby indicating that the residuals were normally distributed with mean 0 and variance σ^2.

However, independence among the residuals was not assured. Often, residuals produced from a regression modelling data taken in time series show a degree of autocorrelation from one week to the next. To adequately address this problem, it became necessary to perform an autoregression on the regression

model, and determine the extent of autocorrelation and the effects of the autocorrelation on the hypothesis tests.

Results of the autoregression (not included in text) indicated a significant amount of correlation between data at one week to data at the previous week (lag-1 autocorrelation). The autoregression also detected a smaller amount of lag-3 correlation stemming from a presently unknown source. The lag-1 correlation indicated that the best predictor for an animal's epinephrine concentration was more the last known epinephrine concentration rather than the time into the study. If the study purpose were to determine a predictive model of epinephrine concentration versus time, this would be a significant find. However, since the study purpose was to determine the effects of RFR on epinephrine concentration, this finding did not significantly change any of the significance tests on the parameters. To adjust for the presence of lag-1 correlation on the parameter tests, a qualitative measure would be to increase the α risk of the conclusion drawn. Since the probability that each epinephrine parameter's F statistic is greater than F_C was better than 0.0001, then this adjustment of α risk would have no practical effect on the conclusion. Thus, although the model had nonindependent characteristics, they were of such a nature as to not affect the final conclusion taken from the model.

To complete the analysis, diagnostics to check for model multicollinearity and correlation between the terms were used. Examination of the listed condition numbers and matrix eigenvalues (being provided under separate cover) detected no troublesome values. This review indicated that the model did not display a significant degree of multicollinearity. Similarly, examination of the correlation matrix showed that correlation between the estimated values of β were all within tolerable limits. The highest degree of correlation was between the x and the x^2 term, which often occurs when using a polynomial model in linear regression.

For future reference, and for the sake of completeness, tables listing animal case number, observations (if taken) at each week, predicted value of epinephrine concentration, standardized error of prediction, 95% confidence intervals on the mean value of the epinephrine concentration, and residuals were prepared, as were tables containing animal case number, regular and studentized residual values, a graphical display of student residual values, and influence statistics (such as Cook's D). These tables were used to detect both outliers and influential data points in the epinephrine data set.

To arrive at a conservative estimate of the *minimum* change due to RFR in resting epinephrine concentrations which this protocol was capable of detecting, the value of the operating curve parameter Φ_B corresponding to the RFR factor (B) discussed at the beginning of the statistical methodology was calculated. This parameter was given by

$$\Phi_B^2 = \frac{naD^2}{2b\sigma^2} \qquad (B\text{-}15)$$

where n = number of replications per cell = 40,

a = number of levels of factor A = 12,

b = number of levels of factor B = 2,

σ^2 = population variance, and

D^2 = detection threshold.

Substituting in values for a, b, n, and the MS_{pe} as an estimate of σ^2. provided an operating curve parameter of

$$\Phi_B = 0.1908\ D. \qquad (B\text{-}16)$$

To obtain a value of Φ from the operating curve, the type I risk α and type II risk β were set to 0.05 and 0.10, respectively. Then, the value of Φ was read from the fixed effects ANOVA curve with $\nu_1 = 1$ and $\nu_2 = 936$. This value was

$$\Phi_B = 2.4. \qquad (B\text{-}17)$$

Degrees of freedom in both numerator and denominator were calculated in the same manner as those in the norepinephrine analysis. Note that the 40 replications in the protocol were not replications in the truest sense of the word (since a single animal was not put through the study 40 times). Since Sprague-Dawley rats represented a very homogeneous population, this difference would have only minor effects on the rigor of this calculation.

The detection level was therefore

$$D_B = 12.58\ pg/mL. \qquad (B\text{-}18)$$

Thus, this protocol conservatively was able to detect an increase in resting plasma epinephrine concentrations of 12.58 pg/mL about 90% of the time.

Plasma Dopamine Statistical Analysis.

Upon examining the scatter diagrams of Figures 10 and 11 and the mean dopamine concentration versus time plot of Figure 12, it did not appear that resting dopamine levels in the exposure group were higher than resting dopamine levels in the sham-exposure group. Therefore, the model to test for RFR-induced effects on dopamine concentration was the starting model of the norepinephrine and epinephrine analyses:

$$y = \beta_0 + \beta_1 x + \beta_{11} x^2 + \alpha_0 z + \alpha_1 zx + \alpha_{11} zx^2 \qquad \text{(B-19)}$$

where y = resting plasma dopamine concentration (in pg/mL),
x = time (in weeks), and
z = a categorical variable with value 0 for animals in the sham-exposure group and value 1 for animals in the exposure group.

The significance of the α terms in this model determined whether or not there were any RFR-induced effects; the algebraic sign of the α then determined whether or not the effects tended to increase resting hormone concentrations (indicated by positive α) or decrease resting hormone concentrations (indicated by negative α). Note that these α terms should not be confused with the symbol for statistical significance (risk), which is also an α.

Data from the dopamine spreadsheets (Appendix L) were subsequently put into a new file and a third SAS formatting program (Appendix M) was prepared to analyze the data.

The model indicated by the forward stepwise and maximum R^2 regression procedures was

$$y = \beta_0 + \beta_1 x + \alpha_1 zx + \beta_{11} x^2 \qquad \text{(B-20)}$$

where $\beta_0 = 51.19$,

$\beta_1 = -3.14$,

$\alpha_1 = -0.92$, and

$\beta_{11} = 0.13$,

with the x, y, and z variables defined as previously. The entry and exit risk were both set to 0.10. The outputs of both regression procedures are included in Appendix N. The absence of α_0 indicated that RFR did not produce a detectable effect on the intercept of the model, and therefore did not bias the dopamine concentration of the exposure group when compared to the sham-exposure group. Equivalently, this showed that at the onset of exposure (week 0), both groups displayed comparable resting dopamine levels. This result was not surprising, since the experiment was designed such that the initial resting dopamine levels of both groups would be similar. Additionally, there was no evidence of any RFR-induced effect on the curvature of the exposure group.

The exposure group did differ from the sham-exposure group with regards to overall time response, however. In both groups, dopamine concentration started out somewhat high (61.8 pg/mL sham-exposure group; 64.6 pg/mL exposure group at week -3). After the initiation of radiation, the exposure group's estimated resting dopamine concentration remained below that of the sham-exposure group for the duration of the study. At week 12, estimated resting dopamine concentrations in sham-exposure animals reached a low value of 32.3 pg/mL; the low for exposure animals was attained at week 16 with an estimated dopamine level of 19.6 pg/mL. The dopamine concentration then rose slightly, reaching estimated values of 35.6 pg/mL in sham-exposure animals and 21.1 pg/mL in exposure animals by week 19 (the final week data were collected) of the study. Both ranges (32.3 to 61.8 pg/mL in sham-exposure animals, 19.6 to 64.6 pg/mL in exposure animals) were still well within the normal range of plasma dopamine in nonstressed male Sprague-Dawley rats (85 $\pm$ 35 pg/mL). Stress in these animals is reflected in an increased rate of dopamine secretion. Therefore, these results indicated that chronic exposure to 435-MHz RFR did not induce an elevation in resting dopamine concentration in the exposure group.

Once again, it was then necessary to check the validity of the assumptions used in building the dopamine regression. First, a model lack-of-fit test was performed (Appendix O). The mean square error and the mean square pure error were 1235.37 and 814.01 respectively, yielding sample standard deviation estimates of 35.15 and 28.53 pg/mL. The calculated value of F_0 was then about 1.51, while the critical value was about 1.38.

Since F_0 exceeded the critical value, the dopamine model displayed a significant lack-of-fit, thereby deviating from results obtained in plasma norepinephrine and plasma epinephrine. The situation was reminiscent of that

encountered in the analysis of ACTH and corticosterone, and in the analysis of prolactin [2,3]. In those cases, significant lack-of-fit was handled by qualitatively altering the significance levels α to compensate for the model defects. This procedure was preferable to transformation of the dependent or independent variables, since a transformation on the dependent variable y would alter the residual distribution and a transformation on the independent variable x, although theoretically possible, would be time consuming and costly and yield a model with minimally better predictive value.

We then decided to follow this course for the dopamine model. Therefore, model lack-of-fit could be deemed statistically significant but practically insignificant by altering the α risk in the coefficients. Since those coefficients were highly significant to begin with, this alteration of α risk should not change the model in any manner.

Residual plots were then generated for the dopamine data. Since no observations in the original data set had values of Cook's D higher than 0.05, we decided not to reject any values from the data set. The residual plots (Appendix P) therefore displayed no obvious patterns or problems. This supported the assumption that the model errors were normally distributed with a mean of zero and a variance of σ^2.

As previously mentioned, the lack of patterns within the residual plots did not guarantee independence within the observations because models produced by regression of data taken in time series tend to show some degree of autocorrelation between the ε_is of each time interval. To adequately address this question, the dopamine data set was reexamined with an autoregressive procedure to determine the extent of residual autocorrelation and its effects on the model's hypothesis tests.

Results of the autoregression (not included in this report) indicated a significant amount of correlation within the data at lags of 1 and 2 weeks (the week 2 autocorrelation was considerably smaller than the week 1 autocorrelation, and stems from a presently unknown source). Once again, this quantitative estimate of autocorrelation was not unexpected, nor practically significant in terms of the conclusions drawn from the model. A further adjustment of the α risk values in the regression would compensate for the lag-1 autocorrelation. Since the probability that each parameter F statistic was greater than the critical F value was better than 0.0003 (for the parameters statistically significant in the dopamine regression), this adjustment of α risk was

inconsequential. Thus, the sheer number of observations taken helped compensate for the model's two main defects: lack-of-fit and nonindependent residuals.

To complete the analysis, diagnostics to check for model multicollinearity and correlation between the terms were used. Examination of the listed condition numbers and matrix eigenvalues (being provided under separate cover) detected no troublesome values and indicated that the model did not display a significant degree of multicollinearity. Similarly, examination of the correlation matrix showed that correlations between the estimated values of β were all within tolerable limits. The highest degree of correlation was between the x and the x^2 term, which often occurs when using a polynomial model in linear regression.

For future reference, and for the sake of completeness, tables listing animal case number, observations (if taken) at each week, predicted value of dopamine concentration, standardized error of prediction, 95% confidence intervals on the mean value of the dopamine concentration, and residuals were prepared, as were tables containing animal case number, regular and studentized residual values, a graphical display of student residual values, and influence statistics (such as Cook's D). These tables were used to detect both outliers and influential data points in the dopamine data set.

To arrive at a conservative estimate of the minimum change due to RFR in resting dopamine concentrations which this protocol was capable of detecting, the value of the operating curve parameter Φ_B corresponding to the RFR factor (B) discussed at the beginning of the statistical methodology was calculated. This parameter was given by

$$\Phi_B^2 = \frac{naD^2}{2b\sigma^2} \qquad \text{(B-21)}$$

where n = number of replications per cell = 40,

a = number of levels of factor A = 12,

b = number of levels of factor B = 2,

σ^2 = population variance, and

D^2 = detection threshold.

Substituting in values for a, b, n, and the MS_{pe} as an estimate of σ^2 provided an operating curve parameter of

$$\Phi_B = 0.3840 \text{ D.} \tag{B-22}$$

To obtain a value of Φ from the operating curve, the type I risk α and type II risk β were set to 0.05 and 0.10, respectively. Then, the value of Φ was read from the fixed effects ANOVA curve with $\nu_1 = 1$ and $\nu_2 = 936$. This value was

$$\Phi_B = 2.4. \tag{B-23}$$

Degrees of freedom in both numerator and denominator were calculated in the same manner as those in the norepinephrine analysis. Once again, the 40 replications in the protocol were not replications in the truest sense (since an individual animal was not put through the study 40 times). However, Sprague-Dawley rats represent a very homogeneous population and thus minimize the between-individual variation of the cell observations.

The detection level was therefore

$$D_B = 6.25 \text{ pg/mL.} \tag{B-24}$$

Thus, the protocol was able to detect an increase in resting plasma dopamine concentrations of 6.25 pg/mL about 90% of the time.

We gratefully acknowledge the assistance of Dr. Russell G. Heikes of Georgia Tech's Department of Industrial and Systems Engineering in developing the statistical methodology of this appendix.

APPENDIX C

NOREPINEPHRINE SAS FORMATTING PROGRAM

```
1          SAS(R) LOG  CMS SAS 5.16       VM/CMS CMS USER QSECLSB

NOTE: COPYRIGHT (C) 1984,1986 SAS INSTITUTE INC., CARY, N.C.  27511, U.S.A.
NOTE: CMS SAS RELEASE 5.16 AT GEORGIA INSTITUTE OF TECHNOLOGY (03559001).

NOTE: CPUID   VERSION = FF  SERIAL = 012242  MODEL = 4381 .

NOTE: SAS OPTIONS SPECIFIED ARE:
      LEAVE=0

  1 DATA TESTN;
  2 CMS FILEDEF X DISK NOREPIN DAT A1;
  3 CMS FILEDEF 20 DISK NOREPIN0 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
  4 CMS FILEDEF 21 DISK NOREPIN1 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
  5 CMS FILEDEF 22 DISK NOREPIN2 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
  6 CMS FILEDEF 23 DISK NOREPIN3 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
  7 CMS FILEDEF 24 DISK NOREPIN4 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
  8 CMS FILEDEF 25 DISK NOREPIN5 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
  9 CMS FILEDEF 26 DISK NOREPIN6 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
 10 CMS FILEDEF 27 DISK NOREPIN7 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
 11 CMS FILEDEF 28 DISK NOREPIN8 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
 12 ARRAY WEEK {24} WKN3 WKN2 MISSN1 WK0-WK20;
 13 KEEP X XSQR Y Z XZ XSQRZ CASE;
 14 INFILE X:
 15 INPUT CASE 1-3
 16       WKN3 5-7
 17       WKN2 9-11
 18       WK0 13-15
 19       WK1 17-19
 20       WK2 21-23
 21       WK3 25-27
 22       WK4 29-31
 23       WK5 33-35
 24       WK6 37-39
 25       WK7 41-43
 26       WK8 45-47
 27       WK9 49-51
 28       WK10 53-55
 29       WK11 57-59
 30       WK12 61-63
 31       WK13 65-67
 32       WK14 69-71
 33       WK15 73-75
 34       WK16 77-79
 35       WK17 81-83
 36       WK18 85-87
 37       WK19 89-91
 38       WK20 93-95
 39 ;
 40 MISSN1=.;
 41 MISS25=.;
 42 MISS27=.;
 43 MISS28=.;
 44 IF CASE < 100 THEN Z = 0;
 45 IF CASE >= 100 THEN Z = 1;
 46 IF Z=1 THEN CASE=CASE-100;
 47 DO I = 1 TO 24;
 48 X = I-4; XSQR = X**X; XZ = X*Z; XSQRZ = X**X*Z; Y = WEEK {I};OUTPUT;
 49 END;
```

```
NOTE: INFILE X IS FILE NOREPIN DAT A1
NOTE: 126 LINES WERE READ FROM INFILE X.
NOTE: DATA SET WORK.TESTN HAS 3024 OBSERVATIONS AND 7 VARIABLES.
NOTE: THE DATA STATEMENT USED 0.61 SECONDS AND 296K.

 50 PROC CONTENTS;
NOTE: THE PROCEDURE CONTENTS USED 0.19 SECONDS AND 424K AND PRINTED PAGES 1 TO 2.

 51 PROC PRINTTO NEW UNIT=20;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 424K.

 52 PROC SORT OUT=SCTR;
 53      BY Z X Y;

NOTE: DATA SET WORK.SCTR HAS 3024 OBSERVATIONS AND 7 VARIABLES.
NOTE: THE PROCEDURE SORT USED 0.72 SECONDS AND 6952K.

 54 PROC SUMMARY;
 55      BY Z X;
 56      VAR Y;
 57      OUTPUT OUT=OVLMN MEAN=MEAN;
NOTE: THE DATA SET WORK.OVLMN HAS 48 OBSERVATIONS AND 5 VARIABLES.
NOTE: THE PROCEDURE SUMMARY USED 0.54 SECONDS AND 424K.

 58 DATA SNOREPIN;
 59      SET SCTR OVLMN;
 60      BY Z;

NOTE: DATA SET WORK.SNOREPIN HAS 3072 OBSERVATIONS AND 10 VARIABLES.
NOTE: THE DATA STATEMENT USED 0.52 SECONDS AND 424K.

 61 PROC PLOT NOLEGEND DATA=SNOREPIN;
 62      BY Z;
 63      PLOT MEAN*X='X' Y*X='.' / VAXIS=90 TO 450 BY 30 OVERLAY;
 64      TITLE 'NOREPINEPHRINE SCATTER DIAGRAM';
NOTE: THE PROCEDURE PLOT USED 1.06 SECONDS AND 424K AND PRINTED PAGES 3 TO 4.

 65 PROC PRINTTO NEW UNIT=21;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 424K.

 66 PROC PLOT NOLEGEND DATA=SNOREPIN;
 67      PLOT MEAN*X='X' / VAXIS=90 TO 450 BY 30;
 68      TITLE 'Mean Norepinephrine Concentration Versus Time';
NOTE: THE PROCEDURE PLOT USED 0.81 SECONDS AND 424K AND PRINTED PAGE 5.

 69 PROC PRINTTO NEW UNIT=22;
 70      TITLE 'CATECHOLAMINE ANALYSIS:  Norepinephrine';

NOTE: THE PROCEDURE PRINTTO USED 0.03 SECONDS AND 424K.

 71 PROC DATASETS;
 72
LIST OF MEMBERS BEFORE UPDATE OF DIRECTORY.
NAME     MEMTYPE            OBS  TRACKS PROT
OVLMN    DATA                48       1
SCTR     DATA              3024       1
```

```
3          SAS(R) LOG  CMS SAS 5.16      VM/CMS CMS USER QSECLSB

SNOREPIN/DATA              3072       1
TESTN   /DATA              3024       1
 72      DELETE SCTR;
 73      DELETE OVLMN;
LIST OF MEMBERS AFTER UPDATE OF DIRECTORY.
NAME    MEMTYPE             OBS  TRACKS PROT
SNOREPIN/DATA              3072       1
TESTN   /DATA              3024       1
NOTE: THE PROCEDURE DATASETS USED 0.12 SECONDS AND 424K.

 74 PROC STEPWISE;
 75      MODEL Y = X XSQR Z XZ XSQRZ /SLENTRY=0.10 SLSTAY=0.10 STEPWISE MAXR;
NOTE: THE PROCEDURE STEPWISE USED 0.63 SECONDS AND 424K AND PRINTED PAGES 6 TO 8.

 76 PROC PRINTTO NEW UNIT=23;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 424K.

 77 PROC REG;
 78      MODEL Y = X XSQR / PARTIAL;
 79      ID CASE;
NOTE: ACOV AND SPEC OPTION ONLY VALID WITH RAWDATA
NOTE: THE PROCEDURE REG USED 1.46 SECONDS AND 744K AND PRINTED PAGES 9 TO 12.

 80 PROC PRINTTO NEW UNIT=24;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 424K.

 81 PROC GLM;
 82      CLASS X Z;
 83      MODEL Y = X X*X X*Z;
NOTE: THE PROCEDURE GLM USED 3.36 SECONDS AND 1128K AND PRINTED PAGES 13 TO 14.

 84 PROC PRINTTO NEW UNIT=25;
 85 *-------------------------------------------------------------------*
 86 *                                                                   *
 87 *     to obtain tables listing the variance inflation factors,      *
 88 *     influence statistics, and tolerances, the following SAS       *
 89 *     statements were used in this partition:                       *
 90 *                                                                   *
 91 *     PROC REG;                                                     *
 92 *          MODEL Y = X XSQR / TOL VIF INFLUENCE;                    *
 93 *          ID CASE;                                                 *
 94 *          OUTPUT OUT=RNOREPIN P=PREDICT R=RESID STUDENT=STUDENT;   *
 95 *                                                                   *
 96 *-------------------------------------------------------------------*;

NOTE: THE PROCEDURE PRINTTO USED 0.04 SECONDS AND 424K.

 97 PROC REG;
 98      MODEL Y = X XSQR / I SS1 SS2 STB COVB CORRB SEQB COLLIN
 99                         COLLINOINT ACOV P R CLM;
100      ID CASE;
101      OUTPUT OUT=RNOREPIN P=PREDICT R=RESID STUDENT=STUDENT;
NOTE: THE DATA SET WORK.RNOREPIN HAS 3072 OBSERVATIONS AND 13 VARIABLES.
NOTE: THE PROCEDURE REG USED 6.76 SECONDS AND 744K AND PRINTED PAGES 15 TO 80.

102 PROC PRINTTO NEW UNIT=26;
```

```
NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 424K.

103 PROC PLOT DATA=RNOREPIN;
104       PLOT RESID*X='*' / VAXIS=-200 TO 200 BY 50;
105       PLOT RESID*PREDICT='*' / HAXIS=220 TO 300 BY 5 VAXIS=-200 TO 200 BY 50;
106       PLOT STUDENT*X='*' / VAXIS=-3 TO 3 BY 0.5;
107       PLOT STUDENT*PREDICT='*' / HAXIS=220 TO 300 BY 5 VAXIS=-3 TO 3 BY 0.5;
108       TITLE 'NOREPINEPHRINE RESIDUAL PLOTS';
NOTE: THE PROCEDURE PLOT USED 1.34 SECONDS AND 424K AND PRINTED PAGES 81 TO 84.

109 PROC PRINTTO NEW UNIT=27;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 424K.

110 PROC PLOT DATA=RNOREPIN;
111       BY Z;
112       PLOT RESID*CASE='*' / VAXIS=-200 TO 200 BY 50 HAXIS=0 TO 65 BY 5;
113       PLOT STUDENT*CASE='*' / VAXIS=-3 TO 3 BY 0.5 HAXIS=0 TO 65 BY 5;
114       TITLE 'NOREPINEPHRINE RESIDUAL PLOTS';
NOTE: THE PROCEDURE PLOT USED 0.74 SECONDS AND 424K AND PRINTED PAGES 85 TO 88.

115 PROC PRINTTO NEW UNIT=28;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 424K.

116 PROC AUTOREG;
117       TITLE 'Norepinephrine Autoregressive Models';
118       MODEL Y = X XSQR / COEF CORRB COVB BACKSTEP;
119       MODEL Y = X XSQR / NLAG=1 COEF CORRB COVB BACKSTEP;
120       MODEL Y = X XSQR / NLAG=2 COEF CORRB COVB BACKSTEP;
121       MODEL Y = X XSQR / NLAG=3 COEF CORRB COVB BACKSTEP;
122       MODEL Y = X XSQR / NLAG=4 COEF CORRB COVB BACKSTEP;
NOTE: THE PROCEDURE AUTOREG USED 6.64 SECONDS AND 424K AND PRINTED PAGES 89 TO 101.
NOTE: SAS USED 6952K MEMORY.

NOTE: SAS INSTITUTE INC.
      SAS CIRCLE
      PO BOX 8000
      CARY, N.C. 27511-8000
```

APPENDIX D

STEPWISE AND MAXIMUM R^2 REGRESSION PROCEDURES USED TO BUILD NOREPINEPHRINE MODEL

STEPWISE REGRESSION PROCEDURE FOR DEPENDENT VARIABLE Y

WARNING: 2409 OBSERVATIONS DELETED DUE TO MISSING VALUES.

STEP 1 VARIABLE X ENTERED R SQUARE = 0.11449742 C(P) = 28.24332231

	DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
REGRESSION	1	393988.32358118	393988.32358118	85.47	0.0001
ERROR	661	3047035.38079288	4609.73582571		
TOTAL	662	3441023.70437406			

	B VALUE	STD ERROR	TYPE II SS	F	PROB>F
INTERCEPT	272.49852493				
X	-3.38385787	0.36602307	393988.32358118	85.47	0.0001

BOUNDS ON CONDITION NUMBER: 1. 1

STEP 2 VARIABLE XSQR ENTERED R SQUARE = 0.14406933 C(P) = 7.29239822

	DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
REGRESSION	2	495745.99146390	247872.99573195	55.55	0.0001
ERROR	660	2945277.71291016	4462.54198926		
TOTAL	662	3441023.70437406			

	B VALUE	STD ERROR	TYPE II SS	F	PROB>F
INTERCEPT	272.83919523				
X	-7.78787472	0.99008634	276104.88323894	61.87	0.0001
XSQR	0.29680630	0.06215566	101757.66788272	22.80	0.0001

BOUNDS ON CONDITION NUMBER: 7.55828, 30.23312

NO OTHER VARIABLES MET THE 0.1000 SIGNIFICANCE LEVEL FOR ENTRY INTO THE MODEL.

SUMMARY OF STEPWISE REGRESSION PROCEDURE FOR DEPENDENT VARIABLE Y

STEP	VARIABLE ENTERED	VARIABLE REMOVED	NUMBER IN	PARTIAL R**2	MODEL R**2	C(P)	F	PROB>F
1	X		1	0.1145	0.1145	28.2433	85.4687	0.0001
2	XSQR		2	0.0296	0.1441	7.2924	22.8026	0.0001

CATECHOLAMINE ANALYSIS: Norepinephrine 9:33 WEDNESDAY, JULY 15, 1987

MAXIMUM R-SQUARE IMPROVEMENT FOR DEPENDENT VARIABLE Y

WARNING: 2409 OBSERVATIONS DELETED DUE TO MISSING VALUES.

STEP 1 VARIABLE X ENTERED R SQUARE = 0.11449742 C(P) = 28.24332231

	DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
REGRESSION	1	393988.32358118	393988.32358118	85.47	0.0001
ERROR	661	3047035.38079288	4609.73582571		
TOTAL	662	3441023.70437406			

	B VALUE	STD ERROR	TYPE II SS	F	PROB>F
INTERCEPT	272.19852493				
X	-3.08385787	0.36602307	393988.32358118	85.47	0.0001

BOUNDS ON CONDITION NUMBER: 1, 1

THE ABOVE MODEL IS THE BEST 1 VARIABLE MODEL FOUND.

STEP 2 VARIABLE XSQR ENTERED R SQUARE = 0.14406933 C(P) = 7.29239822

	DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
REGRESSION	2	495745.99146390	247872.99573195	55.55	0.0001
ERROR	660	2945277.71291016	4462.54198926		
TOTAL	662	3441023.70437406			

	B VALUE	STD ERROR	TYPE II SS	F	PROB>F
INTERCEPT	272.83919523				
X	-7.78787472	0.99008634	276104.88323894	61.87	0.0001
XSQR	0.29680630	0.06215566	101757.66788272	22.80	0.0001

BOUNDS ON CONDITION NUMBER: 7.55828, 30.23312

THE ABOVE MODEL IS THE BEST 2 VARIABLE MODEL FOUND.

STEP 3 VARIABLE XZ ENTERED R SQUARE = 0.14522127 C(P) = 8.39837088

	DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
REGRESSION	3	499709.84651081	166569.94883694	37.32	0.0001
ERROR	659	2941313.85786325	4463.29872210		
TOTAL	662	3441023.70437406			

	B VALUE	STD ERROR	TYPE II SS	F	PROB>F
INTERCEPT	272.79906534				
X	-7.54772938	1.02243501	243230.01739869	54.50	0.0001
XSQR	0.29842352	0.06218462	102791.24459014	23.03	0.0001
XZ	-0.52163781	0.55352617	3963.85504691	0.89	0.3463

BOUNDS ON CONDITION NUMBER: 8.058878, 51.68796

MAXIMUM R-SQUARE IMPROVEMENT FOR DEPENDENT VARIABLE Y

THE ABOVE MODEL IS THE BEST 3 VARIABLE MODEL FOUND.

STEP 4 VARIABLE Z ENTERED R SQUARE = 0.15031078 C(P) = 6.44837554

	DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
REGRESSION	4	517222.96765114	129305.74191278	29.10	0.0001
ERROR	658	2923800.73672292	4443.46616523		
TOTAL	662	3441023.70437406			

	B VALUE	STD ERROR	TYPE II SS	F	PROB>F
INTERCEPT	266.08355576				
X	-7.04498095	1.05112228	199606.66641284	44.92	0.0001
XSQR	0.29589589	0.06205937	101014.81865341	22.73	0.0001
Z	13.38690058	6.74309380	17513.12114033	3.94	0.0475
XZ	-1.43505798	0.71883196	17709.48871269	3.99	0.0463

BOUNDS ON CONDITION NUMBER: 8.555467, 82.15935

THE ABOVE MODEL IS THE BEST 4 VARIABLE MODEL FOUND.

STEP 5 VARIABLE XSQRZ ENTERED R SQUARE = 0.15346548 C(P) = 6.00000000

	DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
REGRESSION	5	528078.34690860	105615.66938172	23.82	0.0001
ERROR	657	2912945.35746546	4433.70678457		
TOTAL	662	3441023.70437406			

	B VALUE	STD ERROR	TYPE II SS	F	PROB>F
INTERCEPT	265.85805427				
X	-5.55978297	1.41540121	68410.61872420	15.43	0.0001
XSQR	0.19548465	0.08922393	21282.84253430	4.80	0.0288
Z	13.61396198	6.73724761	18103.85312935	4.08	0.0437
XZ	-4.31499343	1.97563869	21150.08915658	4.77	0.0293
XSQRZ	0.19411466	0.12405644	10855.37925747	2.45	0.1181

BOUNDS ON CONDITION NUMBER: 20.60071, 367.9338

THE ABOVE MODEL IS THE BEST 5 VARIABLE MODEL FOUND.

APPENDIX E

NOREPINEPHRINE LACK-OF-FIT TEST

CATECHOLAMINE ANALYSIS: Norepinephrine 9:33 WEDNESDAY, JULY 15, 1987

GENERAL LINEAR MODELS PROCEDURE

DEPENDENT VARIABLE: Y

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PR > F	R-SQUARE
MODEL	37	664106.63087876	17948.82786159	4.04	0.0001	0.192997
ERROR	625	2776917.07349530	4443.06731759		ROOT MSE	
CORRECTED TOTAL	662	3441023.70437406			66.65633742	

SOURCE	DF	TYPE I SS	F VALUE	PR > F	DF	TYPE III SS	F VALUE
X	19	565422.75758651	6.70	0.0001	19	531882.23868000	6.30
X*Z	18	98683.87329225	1.23	0.2274	18	98683.87329225	1.23

this term is solely a measure of sum-of-squares pure error.

Partitioning SS_E into SS_{pe} and SS_{lof}

$SS_E = 2945277.71$ df = 660

$SS_{pe} = 2776917.07$ df = 625

$SS_{lof} = 168360.64$ df = 35

$MS_{lof} = 4810.30$

$MS_{pe} = 4443.07$

$$F_o = \frac{MS_{lof}}{MS_{pe}} = 1.0827$$

$F_{0.10,35,625} \sim 1.38$

CATECHOLAMINE ANALYSIS: Norepinephrine

ANALYSIS OF VARIANCE

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PROB>F
MODEL	2	495745.99	247873.00	55.545	0.0001
ERROR	660	2945277.71	4462.54199		
C TOTAL	662	3441023.70			

ROOT MSE	66.80226	R-SQUARE	0.1441
DEP MEAN	252.175	ADJ R-SQ	0.1415
C.V.	26.49044		

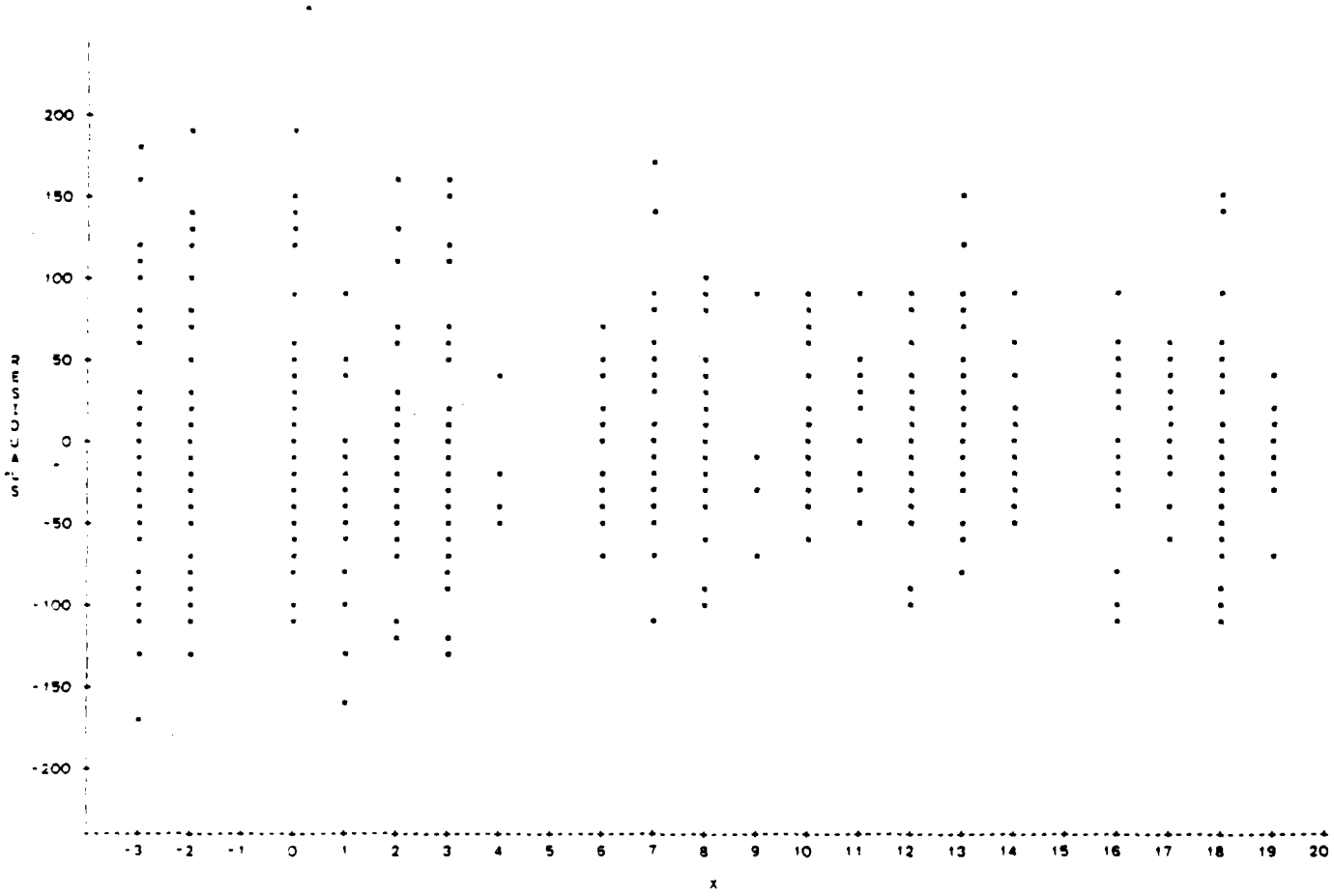
PARAMETER ESTIMATES

VARIABLE	DF	PARAMETER ESTIMATE	STANDARD ERROR	T FOR HO: PARAMETER=0	PROB > |T|
INTERCEP	1	272.83920	3.37851093	80.757	0.0001
X	1	-7.78787472	0.99008634	-7.866	0.0001
XSQR	1	0.29680630	0.06215566	4.775	0.0001

this term contains both sum-of-squares pure error and sum-of-squares lack-of-fit.

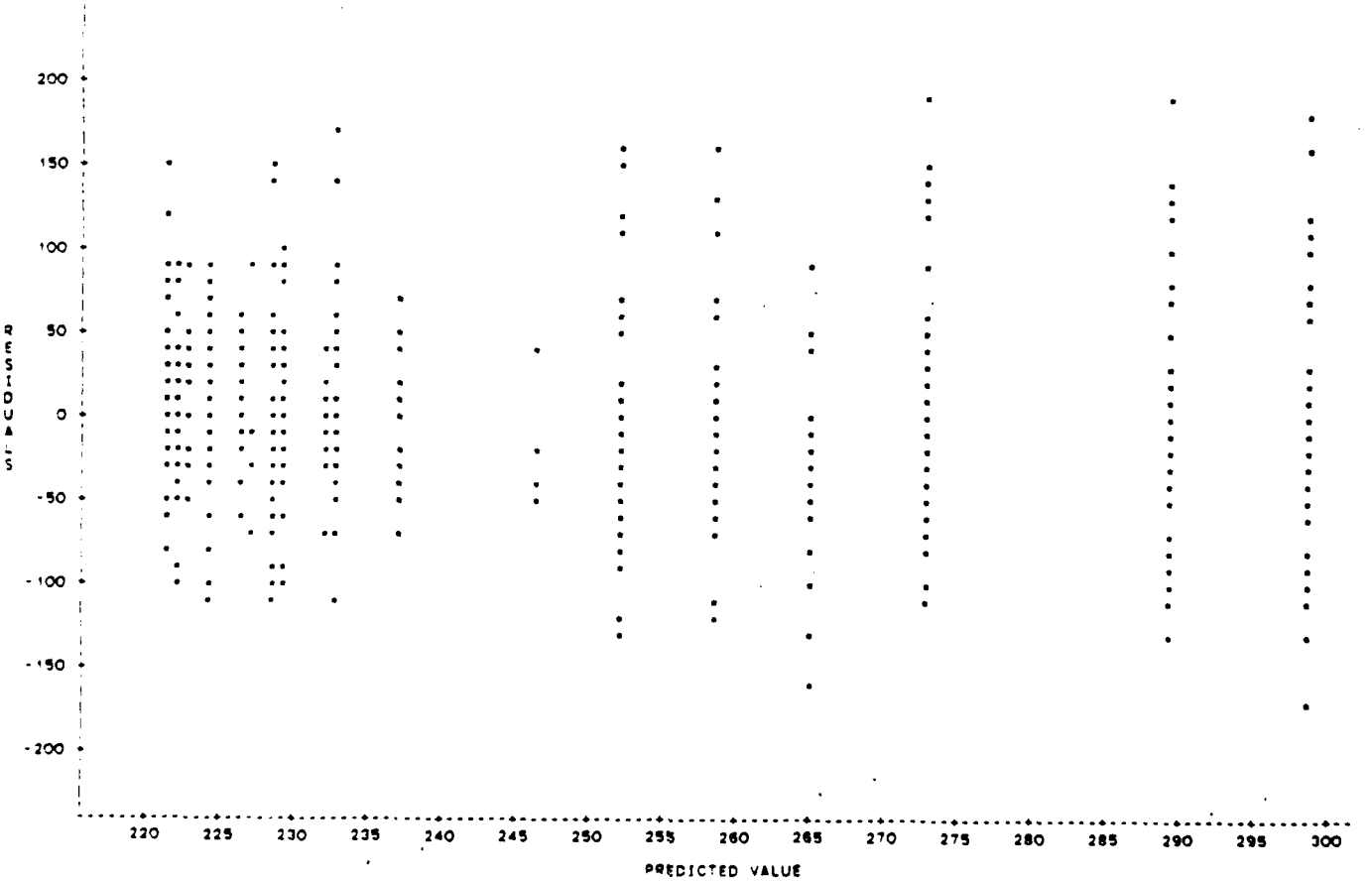
APPENDIX F

NOREPINEPHRINE RESIDUAL PLOTS



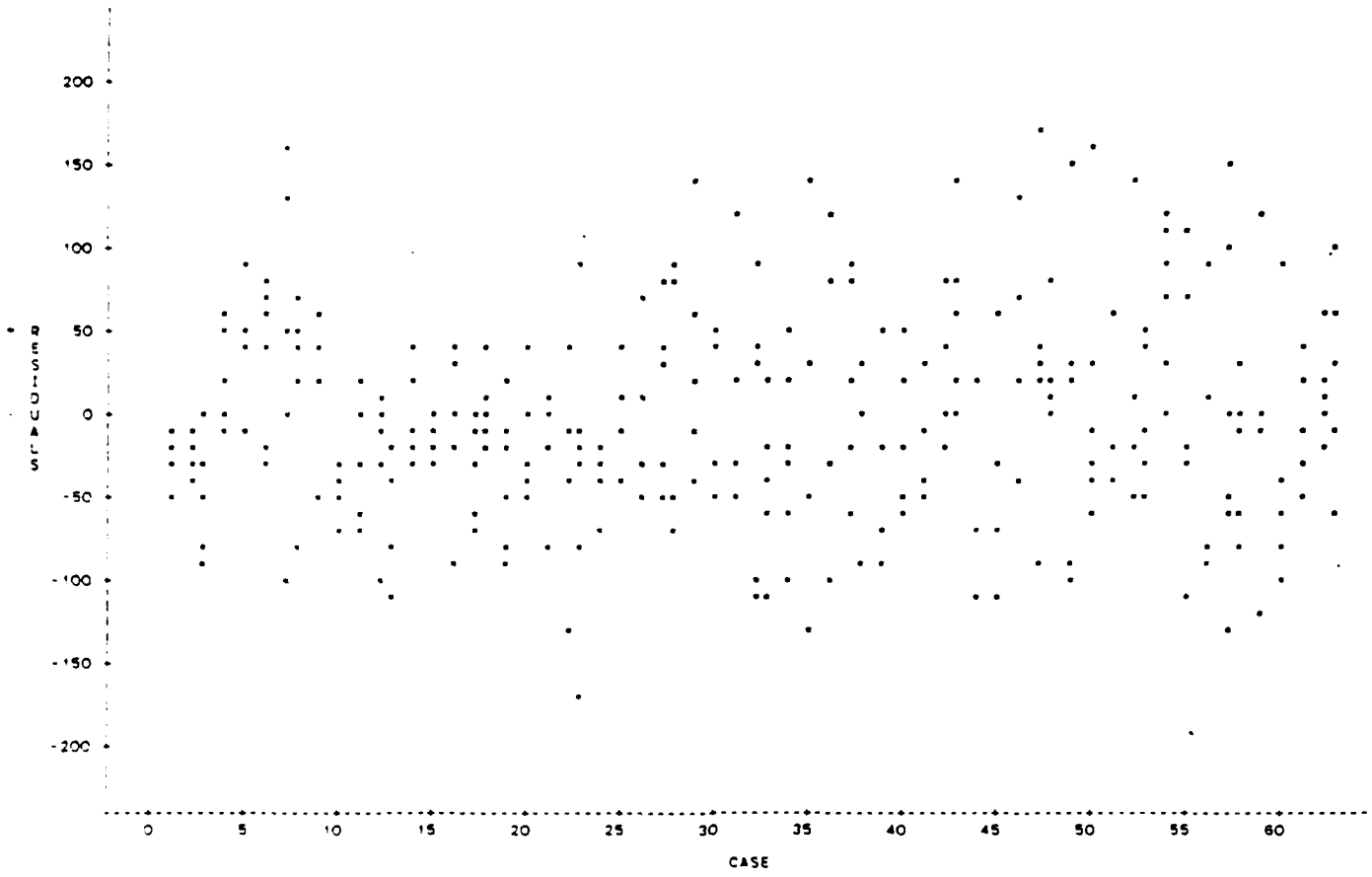
NOTE 2416 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 364 OBS HIDDEN

Residuals versus time.



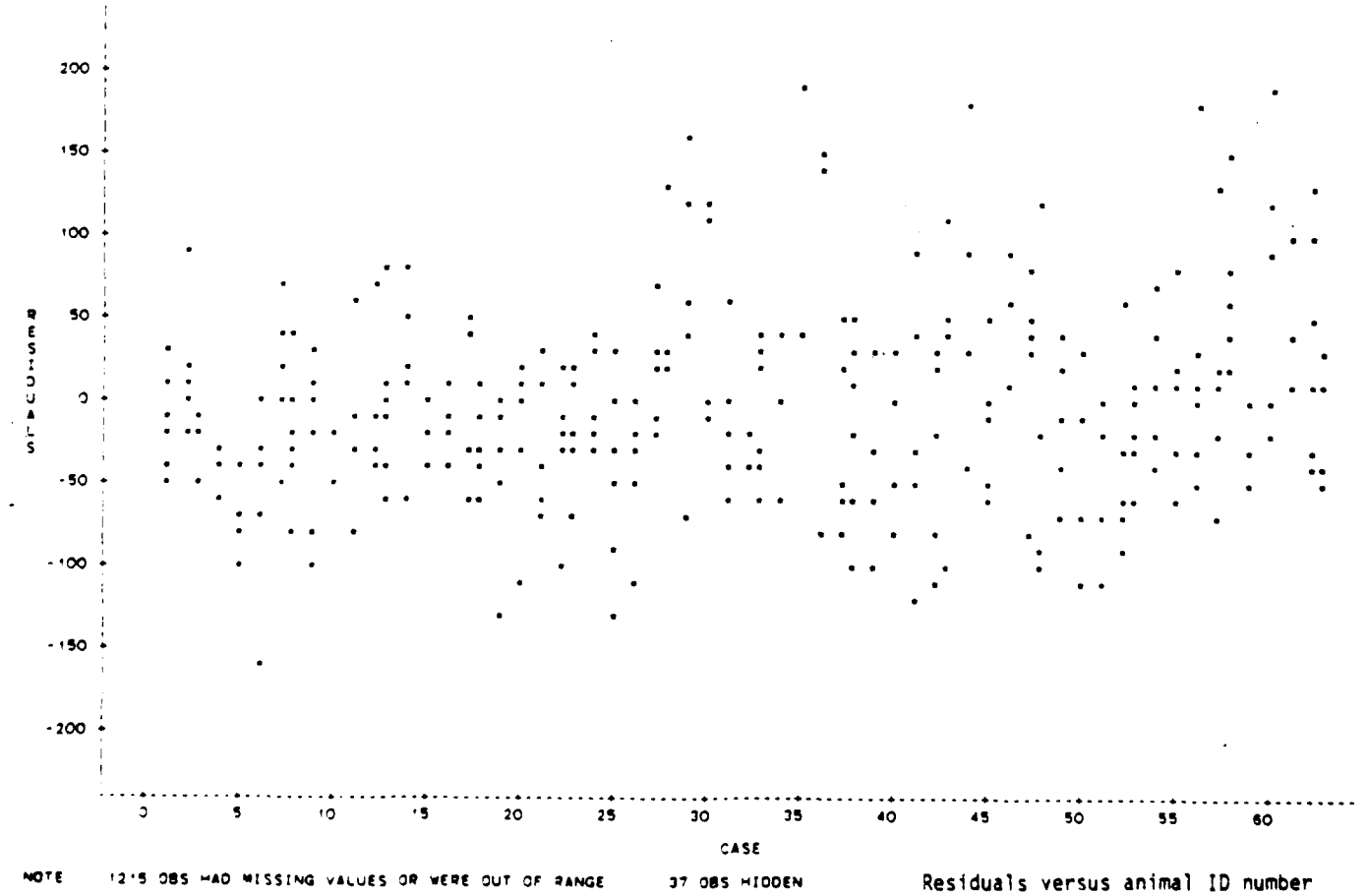
NOTE 2416 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 384 OBS HIDDEN

Residuals versus predicted value of plasma norepinephrine concentration.



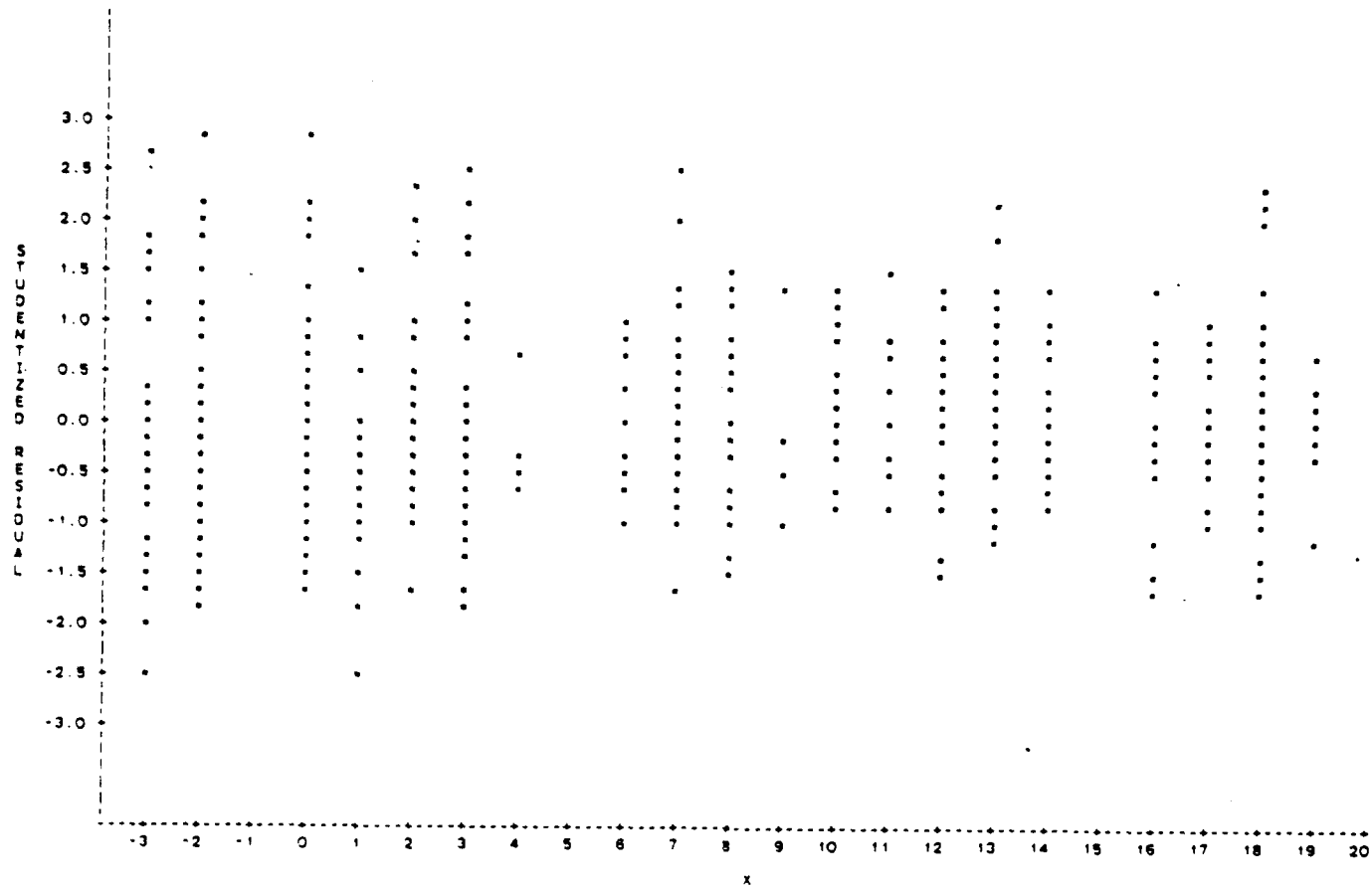
NOTE 1201 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 45 OBS HIDDEN

Residuals versus animal ID number (sham-exposure group).



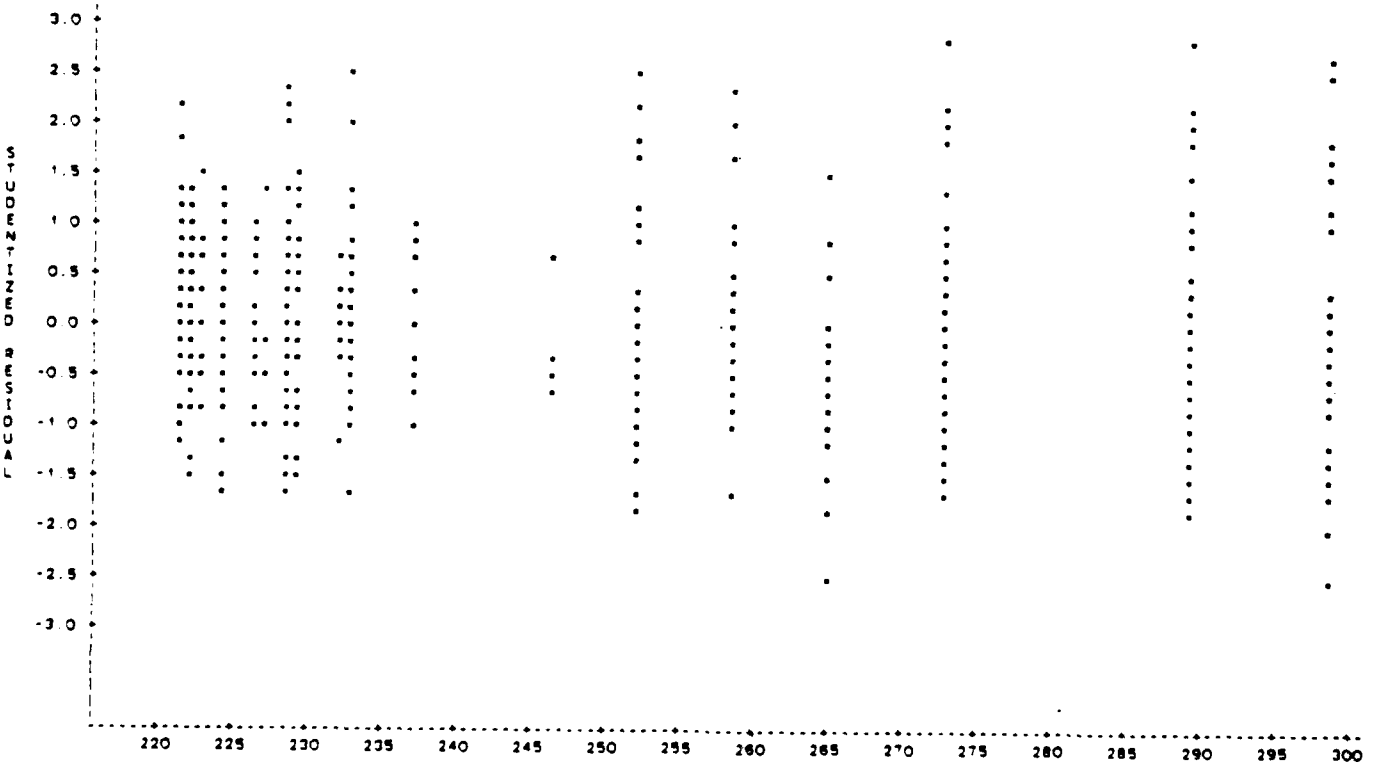
NOTE 1215 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 37 OBS HIDDEN

Residuals versus animal ID number (exposure group).



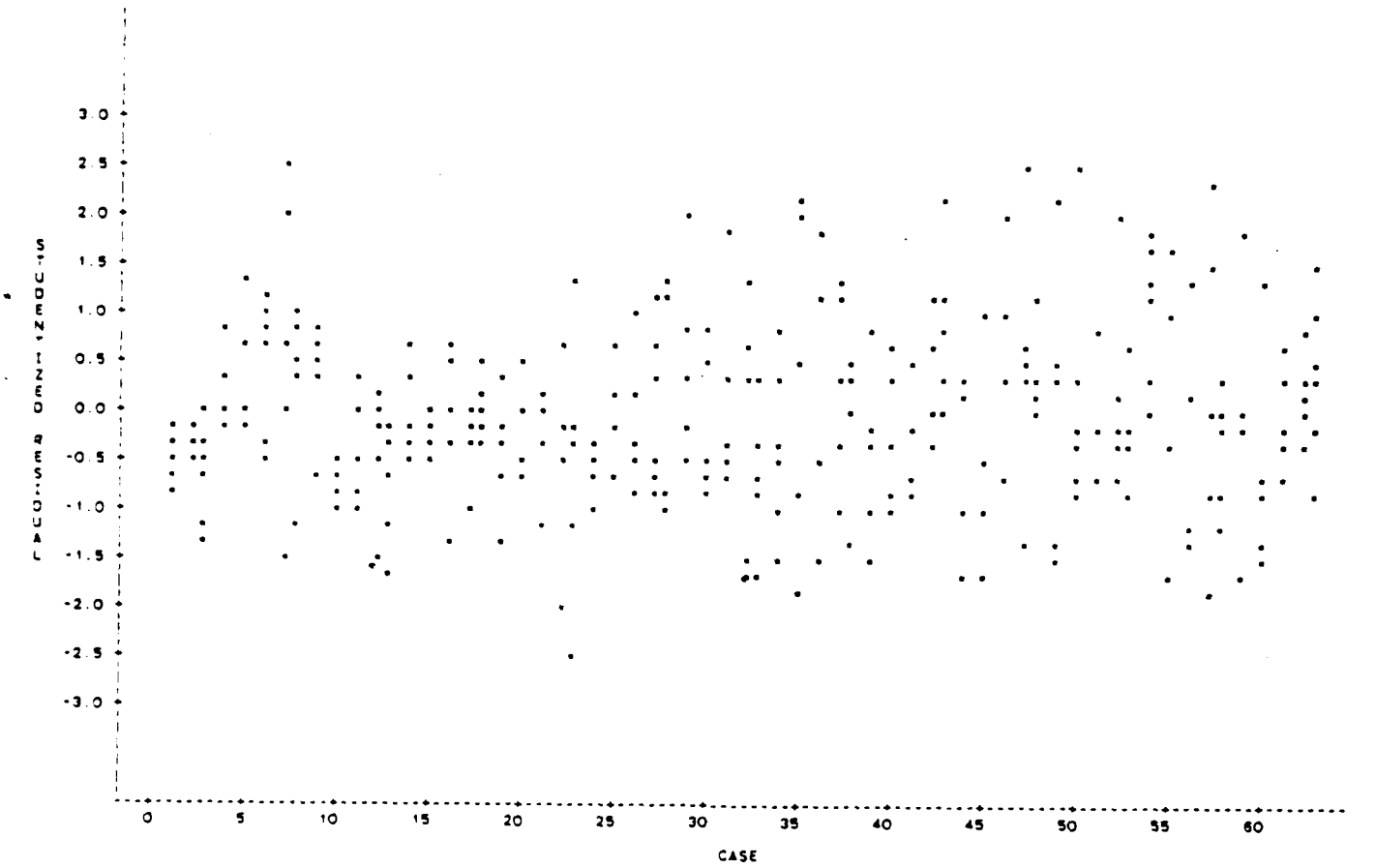
NOTE 2416 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 378 OBS HIDDEN

Studentized residuals versus time.



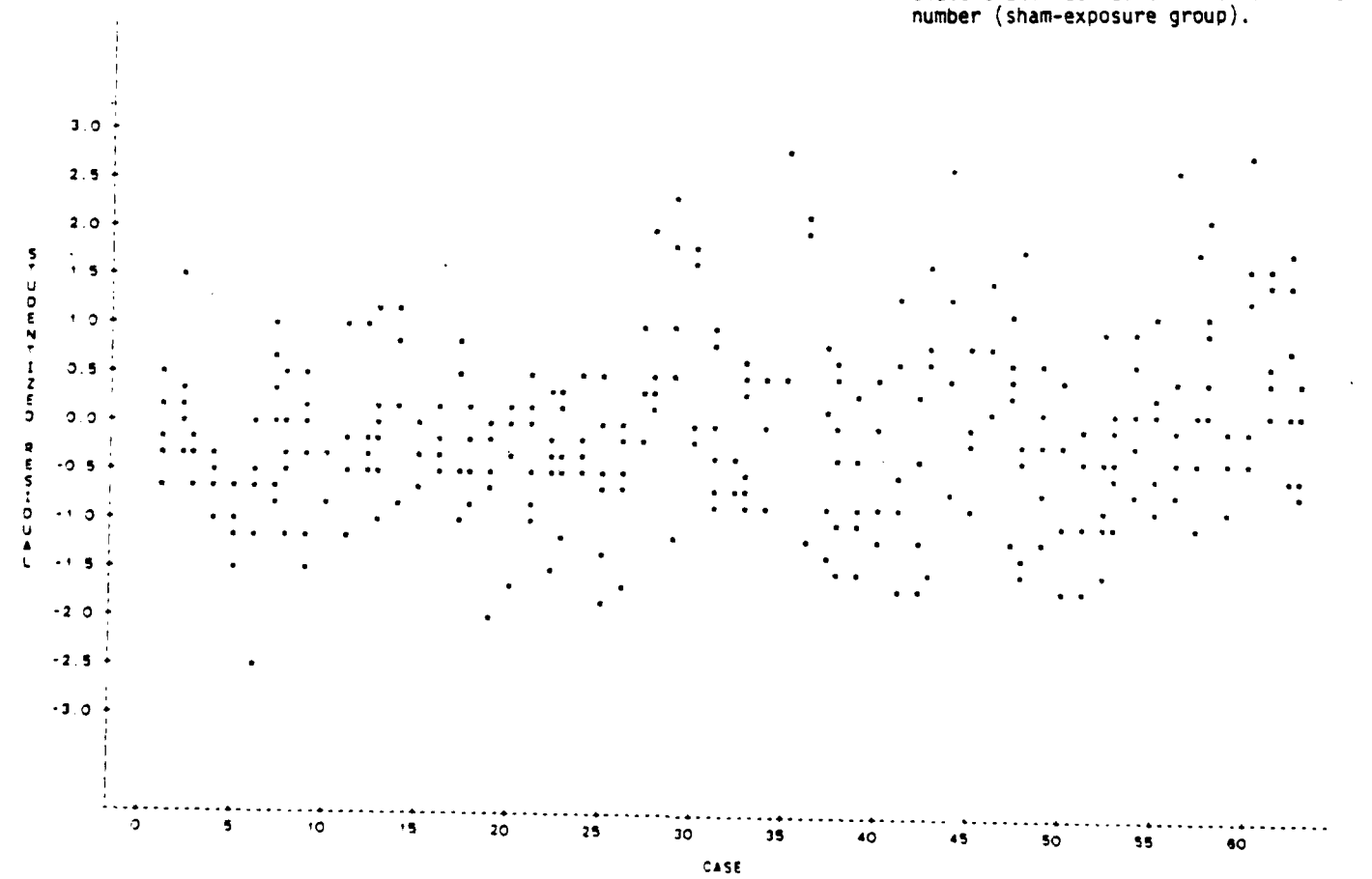
NOTE 2416 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 395 OBS HIDDEN

Studentized residuals versus predicted value of plasma norepinephrine concentration.



NOTE 1201 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 40 OBS HIDDEN

Studentized residuals versus animal ID number (sham-exposure group).



NOTE 1215 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 43 OBS HIDDEN

Studentized residuals versus animal ID number (exposure group).

APPENDIX G

RAW EPINEPHRINE DATA SPREADSHEETS

EPi (pg/ml) Control I

Rat #	Group	-3WK	-2WK	0WK	TIME 1WK	2WK	3WK	4WK	5WK	6WK	7WK	8WK	9WK	10WK	11WK	12WK	13WK	14WK	15WK	16WK	17WK	18WK	19WK	20WK	21WK	22WK	23WK	24WK	+2	+3
1		98		141	140						125			—						129										
2		80		131	117						95			141						143										
3		131		117	101						128			107						130										
4		141		114	96						174			98						—										
5		162		131	114						204			91						145										
6		92		—	82						102			161						129										
7		72		117	31						—			91						87										
8		115		162	90						—			87						—										
9		105		93		74						99				155						45								
10		97		64		152						98				174						93								
11		—		164		181						131				107						79								
12		106		140		95						116				60						74								
13		126		104		112						—				121						118								

EPi (pg/ml) Control II

Rat #	Group	-3WK	-2WK	0WK	TIME 1WK	2WK	3WK	4WK	5WK	6WK	7WK	8WK	9WK	10WK	11WK	12WK	13WK	14WK	15WK	16WK	17WK	18WK	19WK	20WK	21WK	22WK	23WK	24WK	+2	+3
14			142	115		59					209					100						130								
15			151	128		118					127					—						145								
16			130	131		126					—					147						94								
17			315	162		150					138					—						205								
18			71	70		122					120					107						—								
19		—		126		—					211					132						93								
20		246		—		266					180					116						114								
21		165		116		135					105					307						107								
22		150		180			130					91						—					115							
23		—		173			114					—	97					125					—							
24		117		150			95					74						—					110							
25		142		91			—					78						160					104							
26		97		79			95					99						147					113							

EPI (pg/ml) control III

Rat #	Group	-3HR	-2HR	0HR	TIME 1HR	2HR	3HR	4HR	5HR	6HR	7HR	8HR	9HR	10HR	11HR	12HR	13HR	14HR	15HR	16HR	17HR	18HR	19HR	20HR	21HR	22HR	23HR	24HR	+2	+3
27		224		110			150				204					66		160					110							
28		179		185			159				90							99					–							
29		202		167			143				–							147					135							
30		277		–			135				107							205					150							
31		–		117			109				116							140					–							
32		151		207			165				150							–					116							
33		30		184			–				174							116					181							
34		123		–	98						120							–					150							
35			190	185	109						–							–					–							
36			188	131	97						–							–					–							
37			115	164	91						114							145					–							
38			–	137	125						114							207					144							
39			156	124	130						–							64					241							

EPI (pg/ml) Control IV

Rat #	Group	-3HR	-2HR	0HR	TIME 1HR	2HR	3HR	4HR	5HR	6HR	7HR	8HR	9HR	10HR	11HR	12HR	13HR	14HR	15HR	16HR	17HR	18HR	19HR	20HR	21HR	22HR	23HR	24HR	+2	+3
40		204		145		192					–				140					145										
41		–		204		150					121				–					–										
42		–		177		183					187				91					90										
43		207		–		142					–				76					165										
44		211		172		170					–				96					102										
45		211		201		134					117				147					–										
46			–	205		197					122				–					–										
47			117	161		–					122				136					166										
48			190	159		2	111					–				221							–							
49			208	–			92					118				–							–							
50			–	211			–					141				65							202							
51			186	163			106					–				116							185							
52			117	111			151					–				–							–							

EPI (pg/ml) control V

Rat #	Group	-7WK	-2WK	0WK	TIME 1WK	2WK	3WK	4WK	5WK	6WK	7WK	8WK	9WK	10WK	11WK	12WK	13WK	14WK	15WK	16WK	17WK	18WK	19WK	20WK	21WK	22WK	23WK	24WK	+2	+5
53		56		147			118				151						138					161								
54		137		-			85				104						-					215								
55		-		151			105				-						115					-								
56		111		134			126				-						151					194								
57		138		102			-				127						120					97								
58		-		-			104				116						90					-								
59		223	126				-				81						-					-								
60		72	-				116				-						64					180								
61		176	145			83					90					124					215								
62		564	215			193					104					-					114								
63		-	246			-					169					94					99								
64		323	116			100					91					114					65								

EPI (pg/ml) MW I

Rat #	Group	-7WK	-2WK	0WK	TIME 1WK	2WK	3WK	4WK	5WK	6WK	7WK	8WK	9WK	10WK	11WK	12WK	13WK	14WK	15WK	16WK	17WK	18WK	19WK	20WK	21WK	22WK	23WK	24WK	+2	+5
1		167		163	126					121				114			121													
2		191		150	74					-				71			-													
3		97		-	140					162				132			161													
4		173		78	115					-				123			84													
5		218		172	121					123				97			-													
6		166		-	96					134				-			91													
7		122		162	-					134				-			115													
8		166		160	133					-				164			162													
9			-	224		127					360						114					-								
10			230	236		101					-						120					151								
11			140	237		162					-						101					64								
12			-	231		220					134						89					112								
13			144	185		-					112						160					80								

EPI (pg/ml) MW II

Rat #	Group	-2HR	-1HR	0HR	TIME 1HR	2HR	3HR	4HR	5HR	6HR	7HR	8HR	9HR	10HR	11HR	12HR	13HR	14HR	15HR	16HR	17HR	18HR	19HR	20HR	21HR	22HR	23HR	24HR	+2	+3
14		[illegible]	156	128	112					141				241							–										
15			107	120	–					145				106							72										
16			305	142	92					–				112							54										
17		207	–		95					98				–							101										
18		–	71		145					111				–							65										
19		19	–		163					144				–							116										
20		29	24		–					190				123							102										
21		15	62		190					–				118							134										
22		185	–			135					161						–					101									
23		142	136			–					114						–					122									
24		8	–			17					–						114					–									
25		–	221			15					–						–					–									
26		265	213			–					113						124					119									

EPI (pg/ml) MW III

Rat #	Group	-2HR	-1HR	0HR	TIME 1HR	2HR	3HR	4HR	5HR	6HR	7HR	8HR	9HR	10HR	11HR	12HR	13HR	14HR	15HR	16HR	17HR	18HR	19HR	20HR	21HR	22HR	23HR	24HR	+2	+3
27		164		–			165				–								98					121						
28		–		152			181				–								114					134						
29		234		212			176				–								–					121						
30		204		201			–				146								114					–						
31		144		1			125				–								97					88						
32		142		–			161				116						155					91								
33		84		122	11							91					–					113								
34		–		202	33							–					117					121								
35			–	116	24							45					–					115								
36			24	124	–							141					148					–								
37			29	126	35							–					131					160								
38			121	203	–							116					64					162								
39			258	167	201							–					115					113								

EPI (pg/ml) MW IV

Rat #	Group	-3HR	-2HR	0HR	TIME 1HR	2HR	3HR	4HR	5HR	6HR	7HR	8HR	9HR	10HR	11HR	12HR	13HR	14HR	15HR	16HR	17HR	18HR	19HR	20HR	21HR	22HR	23HR	24HR	+2	+5
40		87		192		45					191				61					121										
41		212		124		49					—				89					105										
42		223		—		120					260				—					86										
43		95		216		83					—				114					—										
44		—		117		—					158				167					41										
45		85		192		—					96				112					112										
46			147	—		173					60				—					118										
47			223	116		[illegible]						—				124						64								
48			201	—		79						—				63						—								
49			—	159		165						—				112						34								
50			—	164		75						113				—						118								
51			—	155		164						85				161						164								
52			142	57		101						91				161						181								

EPI (pg/ml) MW V

Rat #	Group	-3HR	-2HR	0HR	TIME 1HR	2HR	3HR	4HR	5HR	6HR	7HR	8HR	9HR	10HR	11HR	12HR	13HR	14HR	15HR	16HR	17HR	18HR	19HR	20HR	21HR	22HR	23HR	24HR	+2	+5
53		129		114			129					157					91					166								
54		120		121			83					191					89					—								
55		63		—			80					—					116					41								
56		147		95			—					211					84					56								
57		[illegible]		[illegible]			—					117					—					86								
58		—		114			161					[illegible]					191					—								
59		162	165				—					41					191					126								
60		—	121					145				—					216					201								
61		122	244					131			—						[illegible]				95									
62		112	57					—			190						34				—									
63		—	114					—			153						[illegible]				114									
64		77	162					80			145						—				161									
65		195	236					160			216						118				—									

APPENDIX H

EPINEPHRINE SAS FORMATTING PROGRAM

```
1          SAS(R) LOG  CMS SAS 5.16      VM/CMS CMS USER QSECLSB

NOTE: COPYRIGHT (C) 1984,1986 SAS INSTITUTE INC., CARY, N.C.  27511, U.S.A.
NOTE: CMS SAS RELEASE 5.16 AT GEORGIA INSTITUTE OF TECHNOLOGY (03559001).

NOTE: CPUID   VERSION = FF  SERIAL = 012242  MODEL = 4381 .

NOTE: SAS OPTIONS SPECIFIED ARE:
      LEAVE=0

  1 DATA TESTE;
  2 CMS FILEDEF X DISK EPIN DAT A1;
  3 CMS FILEDEF 20 DISK EPIN0 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
  4 CMS FILEDEF 21 DISK EPIN1 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
  5 CMS FILEDEF 22 DISK EPIN2 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
  6 CMS FILEDEF 23 DISK EPIN3 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
  7 CMS FILEDEF 24 DISK EPIN4 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
  8 CMS FILEDEF 25 DISK EPIN5 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
  9 CMS FILEDEF 26 DISK EPIN6 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
 10 CMS FILEDEF 27 DISK EPIN7 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
 11 CMS FILEDEF 28 DISK EPIN8 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
 12 ARRAY WEEK {24} WKN3 WKN2 MISSN1 WK0-WK20;
 13 KEEP X XSQR Y Z XZ XSQRZ CASE;
 14 INFILE X;
 15 INPUT CASE 1-3
 16       WKN3 5-7
 17       WKN2 9-11
 18       WK0 13-15
 19       WK1 17-19
 20       WK2 21-23
 21       WK3 25-27
 22       WK4 29-31
 23       WK5 33-35
 24       WK6 37-39
 25       WK7 41-43
 26       WK8 45-47
 27       WK9 49-51
 28       WK10 53-55
 29       WK11 57-59
 30       WK12 61-63
 31       WK13 65-67
 32       WK14 69-71
 33       WK15 73-75
 34       WK16 77-79
 35       WK17 81-83
 36       WK18 85-87
 37       WK19 89-91
 38       WK20 93-95
 39 ;
 40 MISSN1=.;
 41 IF CASE < 100 THEN Z = 0;
 42 IF CASE >= 100 THEN Z = 1;
 43 IF Z=1 THEN CASE=CASE-100;
 44 DO I = 1 TO 24;
 45 X = I-4; XSQR = X*X; XZ = X*Z; XSQRZ = X*X*Z; Y = WEEK {I};OUTPUT;
 46 END;


NOTE: INFILE X IS FILE EPIN DAT A1
NOTE: 129 LINES WERE READ FROM INFILE X.
```

```
2          SAS(R) LOG  CMS SAS 5.16      VM/CMS CMS USER QSECLSB

NOTE: DATA SET WORK.TESTE HAS 3096 OBSERVATIONS AND 7 VARIABLES.
NOTE: THE DATA STATEMENT USED 0.59 SECONDS AND 208K.

 47 PROC CONTENTS;
NOTE: THE PROCEDURE CONTENTS USED 0.20 SECONDS AND 464K AND PRINTED PAGES 1 TO 2.

 48 PROC PRINTTO NEW UNIT=20;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 336K.

 49 PROC SORT OUT=SCTR;
 50      BY Z X Y;

NOTE: DATA SET WORK.SCTR HAS 3096 OBSERVATIONS AND 7 VARIABLES.
NOTE: THE PROCEDURE SORT USED 0.76 SECONDS AND 6928K.

 51 PROC SUMMARY;
 52      BY Z X;
 53      VAR Y;
 54      OUTPUT OUT=OVLMN MEAN=MEAN;
NOTE: THE DATA SET WORK.OVLMN HAS 48 OBSERVATIONS AND 5 VARIABLES.
NOTE: THE PROCEDURE SUMMARY USED 0.56 SECONDS AND 464K.

 55 DATA SEPIN;
 56      SET SCTR OVLMN;
 57      BY Z;

NOTE: DATA SET WORK.SEPIN HAS 3144 OBSERVATIONS AND 10 VARIABLES.
NOTE: THE DATA STATEMENT USED 0.67 SECONDS AND 336K.

 58 PROC PLOT NOLEGEND DATA=SEPIN;
 59      BY Z;
 60      PLOT MEAN*X='X' Y*X='.' / HAXIS=-3 TO 20 BY 1 VAXIS=50 TO 250 BY 25 OVERLAY
 61 ;
 62      TITLE 'EPINEPHRINE SCATTER DIAGRAM';
NOTE: THE PROCEDURE PLOT USED 0.65 SECONDS AND 464K AND PRINTED PAGES 3 TO 4.

 63 PROC PRINTTO NEW UNIT=21;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 336K.

 64 PROC PLOT NOLEGEND DATA=SEPIN;
 65      PLOT MEAN*X='X' / HAXIS=-3 TO 20 BY 1 VAXIS=50 TO 250 BY 25;
 66      TITLE 'Mean Epinephrine Concentration Versus Time';
NOTE: THE PROCEDURE PLOT USED 0.46 SECONDS AND 464K AND PRINTED PAGE 5.

 67 PROC PRINTTO NEW UNIT=22;
 68      TITLE 'CATECHOLAMINE ANALYSIS:  Epinephrine';

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 336K.

 69 PROC DATASETS;
 70
LIST OF MEMBERS BEFORE UPDATE OF DIRECTORY.
NAME     MEMTYPE             OBS   TRACKS PROT
OVLMN    DATA                 48        1
SCTR     DATA               3096        1
SEPIN    DATA               3144        1
```

```
3          SAS(R) LOG  CMS SAS 5.16      VM/CMS CMS USER QSECLSB

TESTE    /DATA             3096       1
 70       DELETE SCTR;
 71       DELETE OVLMN;
LIST OF MEMBERS AFTER UPDATE OF DIRECTORY.
NAME     MEMTYPE            OBS   TRACKS PROT
SEPIN    /DATA             3144       1
TESTE    /DATA             3096       1
NOTE: THE PROCEDURE DATASETS USED 0.12 SECONDS AND 464K.

 72 PROC STEPWISE;
 73       MODEL Y = X XSQR Z XZ XSQRZ / SLENTRY=0.095 SLSTAY=0.095 STEPWISE MAXR;
NOTE: THE PROCEDURE STEPWISE USED 0.57 SECONDS AND 464K AND PRINTED PAGES 6 TO 8.

 74 PROC PRINTTO NEW UNIT=23;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 336K.

 75 PROC REG;
 76       MODEL Y = X XSQR / PARTIAL;
 77       ID CASE;
NOTE: ACOV AND SPEC OPTION ONLY VALID WITH RAWDATA
NOTE: THE PROCEDURE REG USED 1.76 SECONDS AND 656K AND PRINTED PAGES 9 TO 12.

 78 PROC PRINTTO NEW UNIT=24;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 336K.

 79 PROC GLM;
 80       CLASS X Z;
 81       MODEL Y = X X*X X*Z;
NOTE: THE PROCEDURE GLM USED 3.10 SECONDS AND 1040K AND PRINTED PAGES 13 TO 14.

 82 PROC PRINTTO NEW UNIT=25;
 83 *-------------------------------------------------------------------*
 84 *                                                                   *
 85 *     to obtain tables listing the variance inflation factors,      *
 86 *     influence statistics, and tolerances, the following SAS       *
 87 *     statements were used in this partition:                       *
 88 *                                                                   *
 89 *     PROC REG;                                                     *
 90 *          MODEL Y = X XSQR / TOL VIF INFLUENCE;                    *
 91 *          ID CASE;                                                 *
 92 *          OUTPUT OUT=REPIN P=PREDICT R=RESID STUDENT=STUDENT;      *
 93 *                                                                   *
 94 *-------------------------------------------------------------------*;

NOTE: THE PROCEDURE PRINTTO USED 0.04 SECONDS AND 336K.

 95 PROC REG;
 96       MODEL Y = X XSQR / I SS1 SS2 STB COVB CORRB SEQB COLLIN
 97                          COLLINOINT ACOV P R CLM;
 98       ID CASE;
 99       OUTPUT OUT=REPIN P=PREDICT R=RESID STUDENT=STUDENT;
NOTE: THE DATA SET WORK.REPIN HAS 3144 OBSERVATIONS AND 13 VARIABLES.
NOTE: THE PROCEDURE REG USED 6.93 SECONDS AND 656K AND PRINTED PAGES 15 TO 82.

100 PROC PRINTTO NEW UNIT=26;
```

```
4          SAS(R) LOG  CMS SAS 5.16      VM/CMS CMS USER QSECLSB

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 336K.

101 PROC PLOT DATA=REPIN;
102       PLOT RESID*X='*' / HAXIS=-3 TO 20 BY 1 VAXIS=-150 TO 150 BY 25;
103       PLOT RESID*PREDICT='*' / HAXIS=115 TO 185 BY 5 VAXIS=-150 TO 150 BY 25;
104       PLOT STUDENT*X='*' / HAXIS=-3 TO 20 BY 1 VAXIS=-4 TO 5 BY 0.5;
105       PLOT STUDENT*PREDICT='*' / HAXIS=115 TO 185 BY 5 VAXIS=-4 TO 5 BY 0.5;
106       TITLE 'EPINEPHRINE RESIDUAL PLOTS';
NOTE: THE PROCEDURE PLOT USED 0.95 SECONDS AND 464K AND PRINTED PAGES 83 TO 86.

107 PROC PRINTTO NEW UNIT=27;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 336K.

108 PROC PLOT DATA=REPIN;
109       BY Z;
110       PLOT RESID*CASE='*' / HAXIS=0 TO 65 BY 5 VAXIS=-150 TO 150 BY 25;
111       PLOT STUDENT*CASE='*' / HAXIS=0 TO 65 BY 5 VAXIS=-4 TO 5 BY 0.5;
112       TITLE 'EPINEPHRINE RESIDUAL PLOTS';
NOTE: THE PROCEDURE PLOT USED 0.79 SECONDS AND 464K AND PRINTED PAGES 87 TO 90.

113 PROC PRINTTO NEW UNIT=28;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 336K.

114 PROC AUTOREG;
115       TITLE 'Epinephrine Autoregressive Models';
116       MODEL Y = X XSQR / COEF CORRB COVB BACKSTEP;
117       MODEL Y = X XSQR / NLAG=1 COEF CORRB COVB BACKSTEP;
118       MODEL Y = X XSQR / NLAG=2 COEF CORRB COVB BACKSTEP;
119       MODEL Y = X XSQR / NLAG=3 COEF CORRB COVB BACKSTEP;
120       MODEL Y = X XSQR / NLAG=4 COEF CORRB COVB BACKSTEP;
NOTE: THE PROCEDURE AUTOREG USED 6.92 SECONDS AND 464K AND PRINTED PAGES 91 TO 103.
NOTE: SAS USED 6928K MEMORY.

NOTE: SAS INSTITUTE INC.
      SAS CIRCLE
      PO BOX 8000
      CARY, N.C. 27511-8000
```

APPENDIX I

STEPWISE AND MAXIMUM R^2 REGRESSION PROCEDURES USED TO BUILD EPINEPHRINE MODEL

STEPWISE REGRESSION PROCEDURE FOR DEPENDENT VARIABLE Y

WARNING: 2550 OBSERVATIONS DELETED DUE TO MISSING VALUES.

STEP 1 VARIABLE X ENTERED R SQUARE = 0.08730405 C(P) = 35.09383984

	DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
REGRESSION	1	197141.55027836	197141.55027836	56.63	0.0001
ERROR	592	2060961.61470481	3481.35407889		
TOTAL	593	2258103.16498316			

	B VALUE	STD ERROR	TYPE II SS	F	PROB>F
INTERCEPT	158.81632525				
X	-2.55984031	0.34017147	197141.55027836	56.63	0.0001

BOUNDS ON CONDITION NUMBER: 1, 1

STEP 2 VARIABLE XSQR ENTERED R SQUARE = 0.12078896 C(P) = 14.16045333

	DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
REGRESSION	2	272753.92439253	136376.96219626	40.60	0.0001
ERROR	591	1985349.24059064	3359.30497562		
TOTAL	593	2258103.16498316			

	B VALUE	STD ERROR	TYPE II SS	F	PROB>F
INTERCEPT	158.79893544				
X	-6.66208019	0.92698997	173507.82846438	51.65	0.0001
XSQR	0.28169664	0.05937586	75612.37411417	22.51	0.0001

BOUNDS ON CONDITION NUMBER: 7.695787, 30.78315

NO OTHER VARIABLES MET THE 0.0950 SIGNIFICANCE LEVEL FOR ENTRY INTO THE MODEL.

SUMMARY OF STEPWISE REGRESSION PROCEDURE FOR DEPENDENT VARIABLE Y

STEP	VARIABLE ENTERED	VARIABLE REMOVED	NUMBER IN	PARTIAL R**2	MODEL R**2	C(P)	F	PROB>F
1	X		1	0.0873	0.0873	35.0938	56.6278	0.0001
2	XSQR		2	0.0335	0.1208	14.1605,	22.5083	0.0001

CATECHOLAMINE ANALYSIS: Epinephrine 9:41 WEDNESDAY, JULY 15, 1987

MAXIMUM R-SQUARE IMPROVEMENT FOR DEPENDENT VARIABLE Y

WARNING: 2550 OBSERVATIONS DELETED DUE TO MISSING VALUES.

STEP 1 VARIABLE X ENTERED R SQUARE = 0.08730405 C(P) = 35.09383984

	DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
REGRESSION	1	197141.55027836	197141.55027836	56.63	0.0001
ERROR	592	2060961.61470481	3481.35407889		
TOTAL	593	2258103.16498316			

	B VALUE	STD ERROR	TYPE II SS	F	PROB>F
INTERCEPT	158.81632525				
X	-2.55984031	0.34017147	197141.55027836	56.63	0.0001

BOUNDS ON CONDITION NUMBER: 1, 1

THE ABOVE MODEL IS THE BEST 1 VARIABLE MODEL FOUND.

STEP 2 VARIABLE XSQR ENTERED R SQUARE = 0.12078896 C(P) = 14.16045333

	DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
REGRESSION	2	272753.92439253	136376.96219626	40.60	0.0001
ERROR	591	1985349.24059064	3359.30497562		
TOTAL	593	2258103.16498316			

	B VALUE	STD ERROR	TYPE II SS	F	PROB>F
INTERCEPT	158.79893544				
X	-6.66208019	0.92698997	173507.82846438	51.65	0.0001
XSQR	0.28169664	0.05937586	75612.37411417	22.51	0.0001

BOUNDS ON CONDITION NUMBER: 7.695787, 30.78315

THE ABOVE MODEL IS THE BEST 2 VARIABLE MODEL FOUND.

STEP 3 VARIABLE Z ENTERED R SQUARE = 0.12483461 C(P) = 13.38963753

	DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
REGRESSION	3	281889.42478648	93963.14159549	28.05	0.0001
ERROR	590	1976213.74019668	3349.51481389		
TOTAL	593	2258103.16498316			

	B VALUE	STD ERROR	TYPE II SS	F	PROB>F
INTERCEPT	154.93778668				
X	-6.63711697	0.92576161	172164.06521280	51.40	0.0001
XSQR	0.27971980	0.05930136	74524.48285659	22.25	0.0001
Z	7.84556183	4.75060400	9135.50039395	2.73	0.0992

BOUNDS ON CONDITION NUMBER: 7.698924, 49.19166

MAXIMUM R-SQUARE IMPROVEMENT FOR DEPENDENT VARIABLE Y

THE ABOVE MODEL IS THE BEST 3 VARIABLE MODEL FOUND.

STEP 4 VARIABLE XZ ENTERED R SQUARE = 0.14101088 C(P) = 4.31071813

	DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
REGRESSION	4	318417.10455811	79604.27613953	24.17	0.0001
ERROR	589	1939686.06042506	3293.18516201		
TOTAL	593	2258103.16498316			

	B VALUE	STD ERROR	TYPE II SS	F	PROB>F
INTERCEPT	148.62241564				
X	-5.43217501	0.98666994	99820.52761921	30.31	0.0001
XSQR	0.27336090	0.05883160	71099.68782579	21.59	0.0001
Z	20.47384481	6.04699754	37751.60148760	11.46	0.0008
XZ	-2.20506461	0.66209202	36527.67977163	11.09	0.0009

BOUNDS ON CONDITION NUMBER: 8.893651, 83.71208

THE ABOVE MODEL IS THE BEST 4 VARIABLE MODEL FOUND.

STEP 5 VARIABLE XSQRZ ENTERED R SQUARE = 0.14146455 C(P) = 6.00000000

	DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
REGRESSION	5	319441.55576601	63888.31115320	19.38	0.0001
ERROR	588	1938661.60921715	3297.04355309		
TOTAL	593	2258103.16498316			

	B VALUE	STD ERROR	TYPE II SS	F	PROB>F
INTERCEPT	148.67993274				
X	-5.90883059	1.30608930	67481.07929095	20.47	0.0001
XSQR	0.30568514	0.08263127	45121.59874017	13.69	0.0002
Z	20.48053628	6.05055083	37776.13355382	11.46	0.0008
XZ	-1.24939073	1.83799887	1523.45896043	0.46	0.4969
XSQRZ	-0.06563374	0.11774537	1024.45120791	0.31	0.5775

BOUNDS ON CONDITION NUMBER: 20.6184, 363.4548

THE ABOVE MODEL IS THE BEST 5 VARIABLE MODEL FOUND.

APPENDIX J

EPINEPHRINE LACK-OF-FIT TEST

CATECHOLAMINE ANALYSIS: Epinephrine 9:41 WEDNESDAY, JULY 15, 1987

GENERAL LINEAR MODELS PROCEDURE

DEPENDENT VARIABLE: Y

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PR > F	R-SQUARE
MODEL	37	425141.48629790	11490.31044048	3.49	0.0001	0.188274
ERROR	556	1832961.67868527	3296.69366670		ROOT MSE	
CORRECTED TOTAL	593	2258103.16498317			57.41684132	

SOURCE	DF	TYPE I SS	F VALUE	PR > F	DF	TYPE III SS	F VALUE
X	19	348054.66052419	5.56	0.0001	19	328774.50250746	5.25
X*Z	18	77086.82577371	1.30	0.1818	18	77086.82577371	1.30

this term is solely a measure of sum-of-squares pure error.

Partitioning SS_E into SS_{pe} and SS_{lof}

$SS_E = 1985349.24$ $df = 591$

$SS_{pe} = 1832961.68$ $df = 556$

$SS_{lof} = 152387.56$ $df = 35$

$MS_{lof} = 4353.93$

$MS_{pe} = 3296.69$

$$F_o = \frac{MS_{lof}}{MS_{pe}} = 1.3207$$

$F_{0.10,35,556} \approx 1.38$

CATECHOLAMINE ANALYSIS: Epinephrine

ANALYSIS OF VARIANCE

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PROB>F
MODEL	2	272753.92	136376.96	40.597	0.0001
ERROR	591	1985349.24	3359.30498		
C TOTAL	593	2258103.16			

ROOT MSE	57.95951	R-SQUARE	0.1208
DEP MEAN	144.1684	ADJ R-SQ	0.1178
C.V.	40.20266		

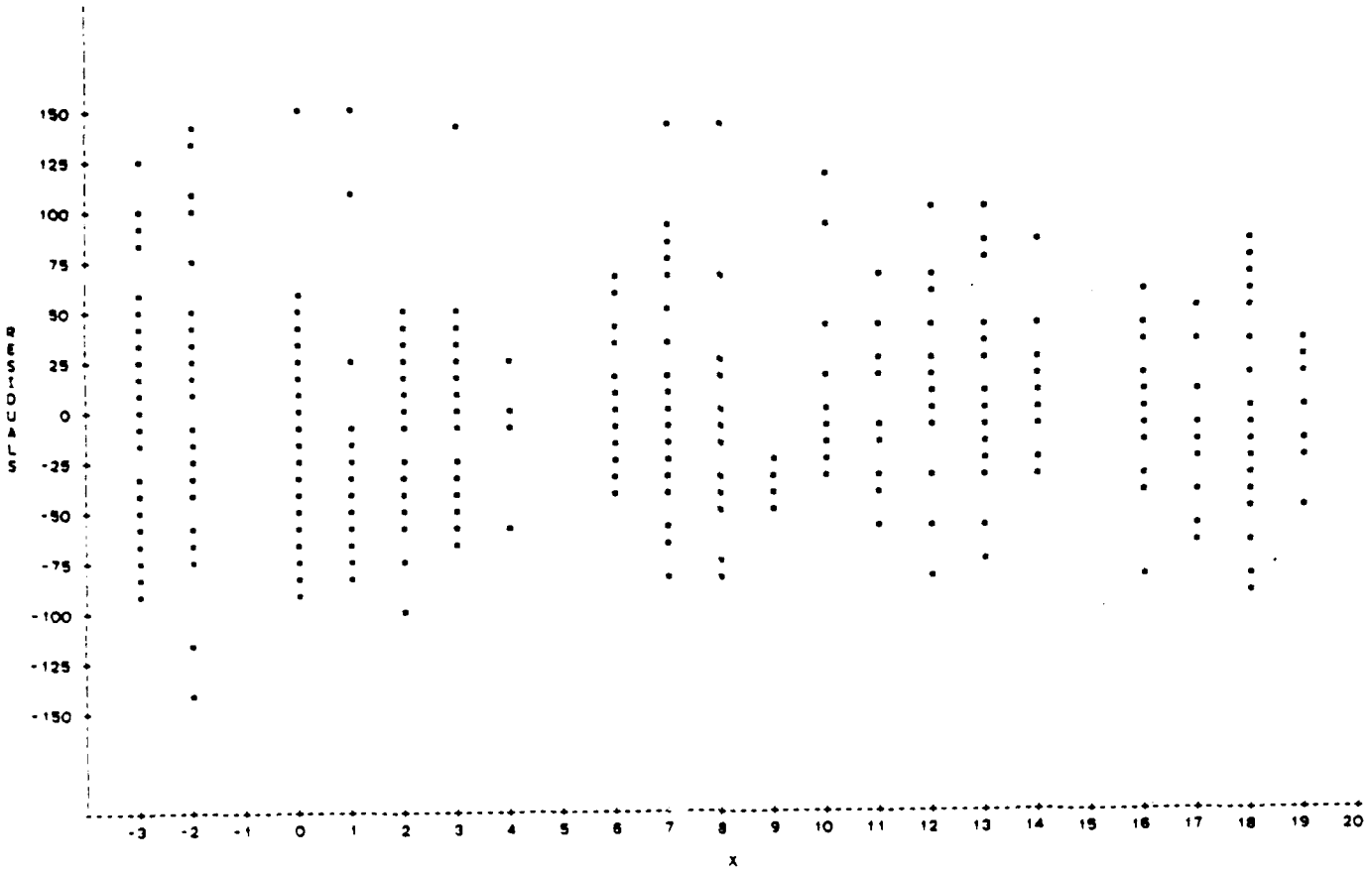
PARAMETER ESTIMATES

VARIABLE	DF	PARAMETER ESTIMATE	STANDARD ERROR	T FOR HO: PARAMETER=0	PROB > |T|
INTERCEP	1	158.79894	3.05148810	52.040	0.0001
X	1	-6.66208019	0.92698997	-7.187	0.0001
XSQR	1	0.28169664	0.05937586	4.744	0.0001

this term contains both sum-of-squares pure error and sum-of-squares lack-of-fit.

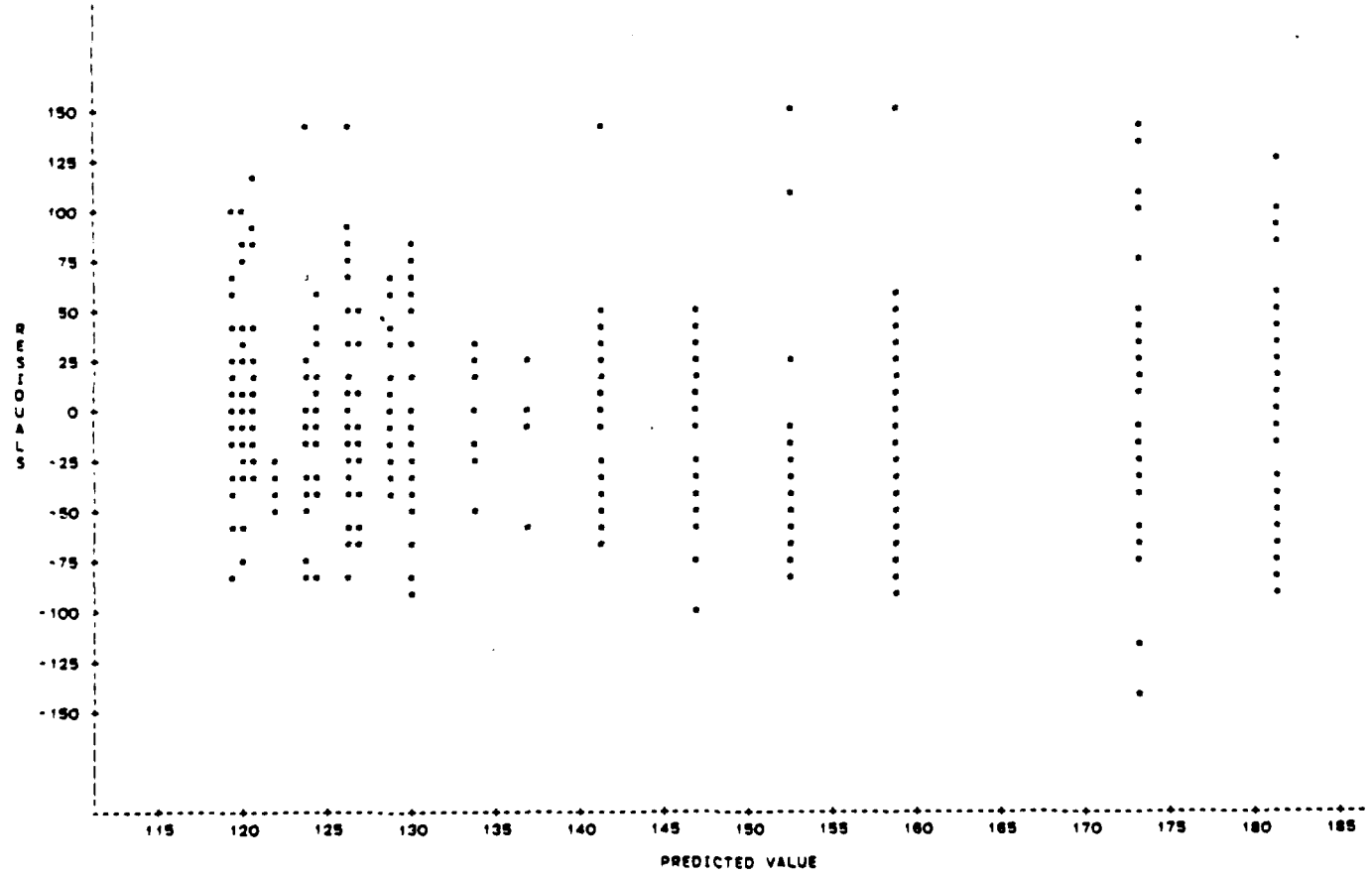
APPENDIX K

EPINEPHRINE RESIDUAL PLOTS



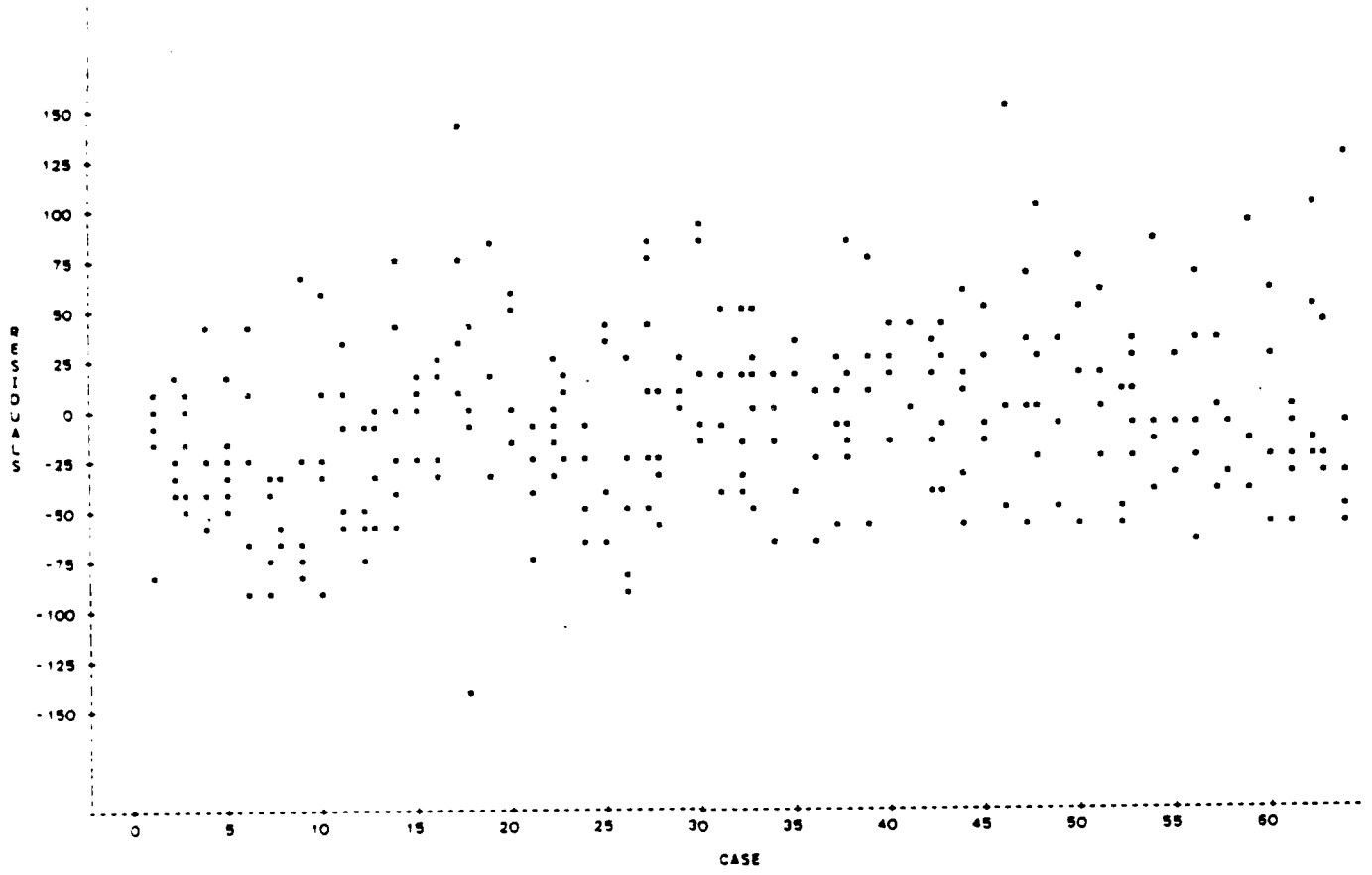
NOTE 2562 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 329 OBS HIDDEN

Residuals versus time.



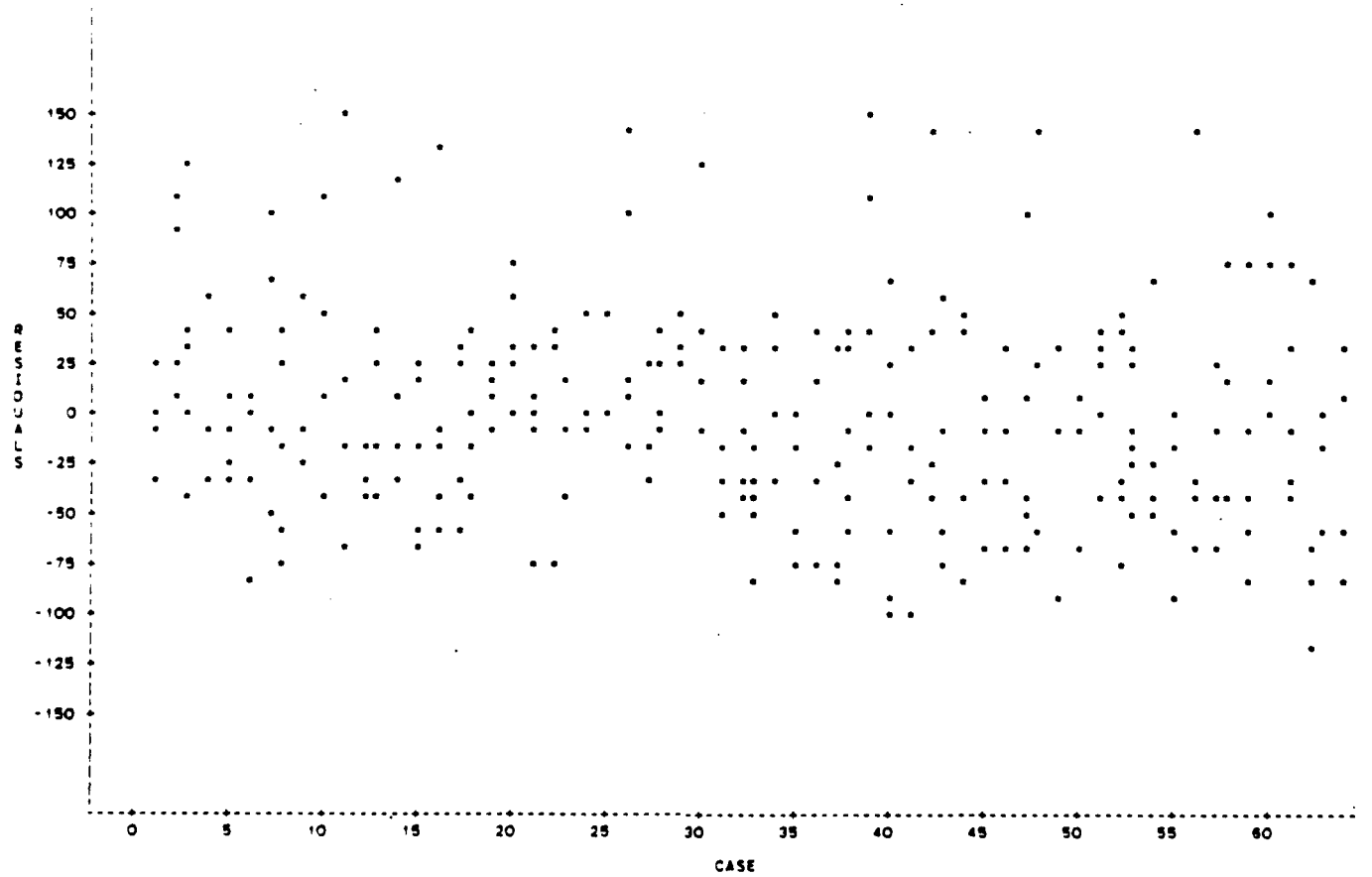
NOTE 2562 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 342 OBS HIDDEN

Residuals versus predicted value of plasma epinephrine concentration.



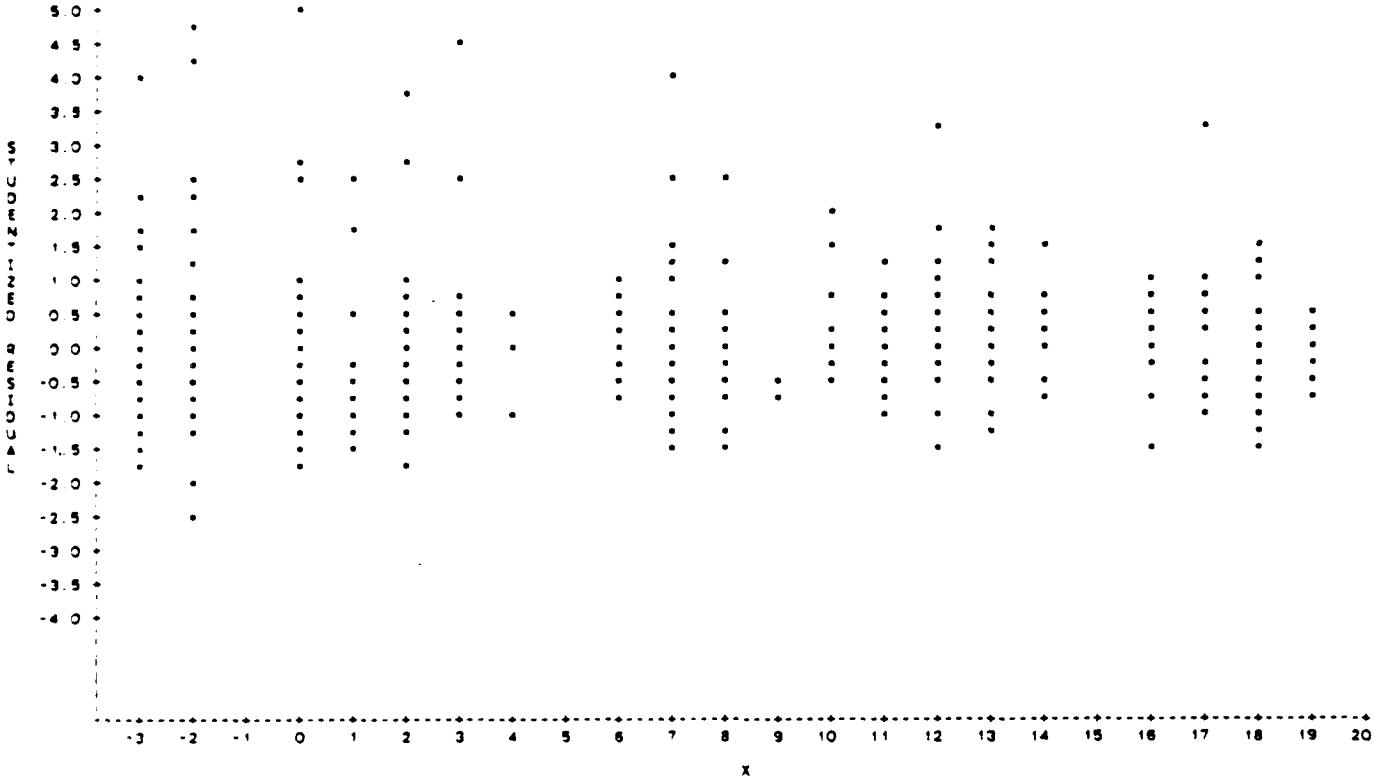
NOTE 1265 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 33 OBS HIDDEN

Residuals versus animal ID number (*sham*-exposure group).



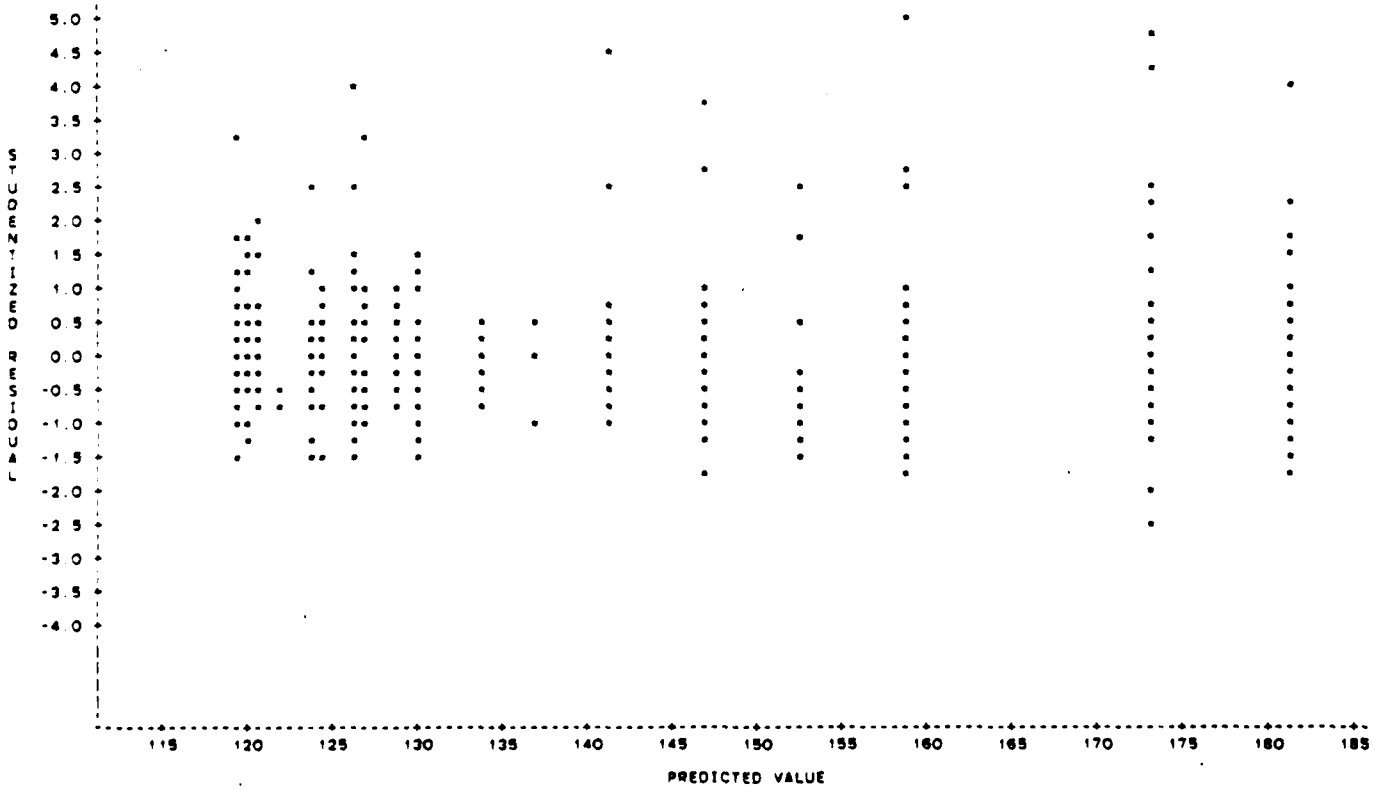
NOTE 1297 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 20 OBS HIDDEN

Residuals versus animal ID number (exposure group).



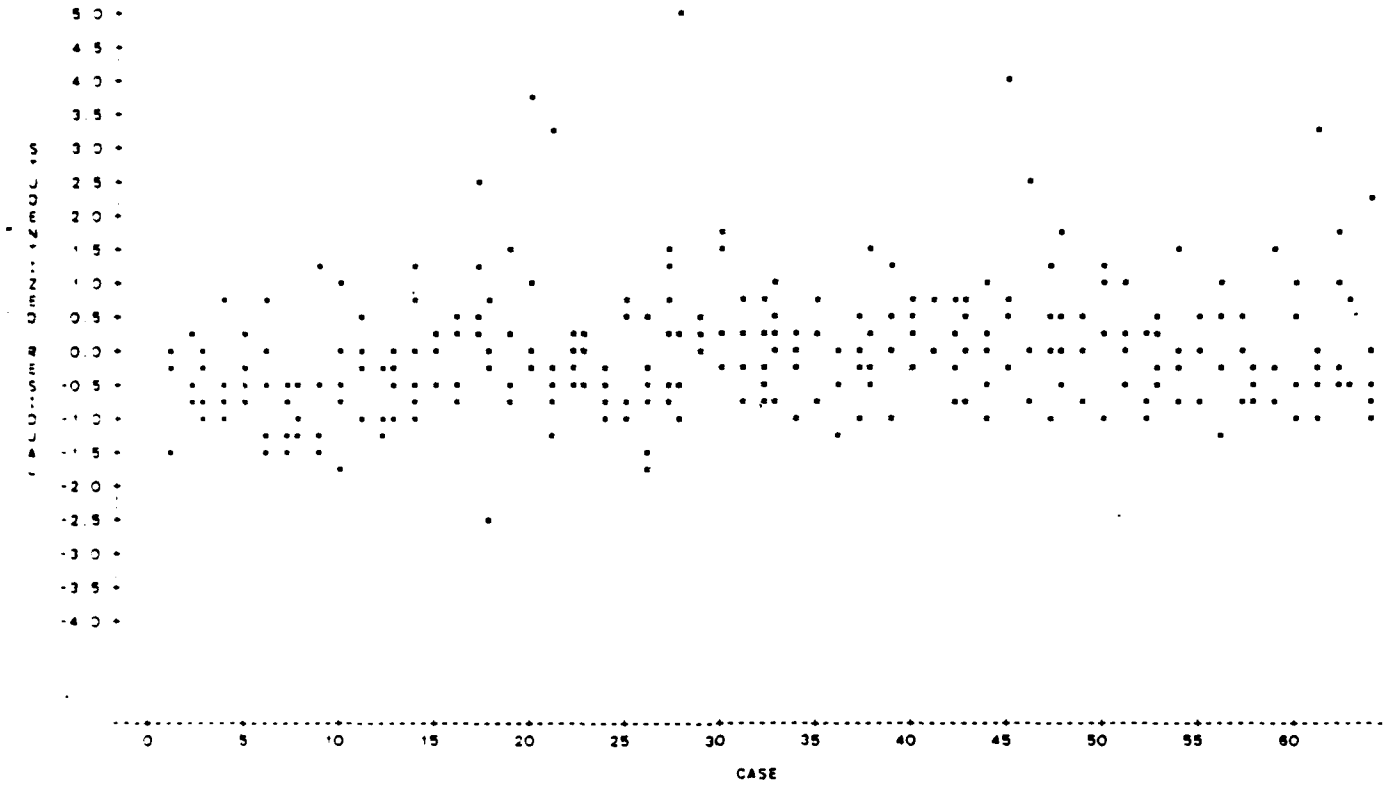
NOTE 2550 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 396 OBS HIDDEN

Studentized residuals versus time.



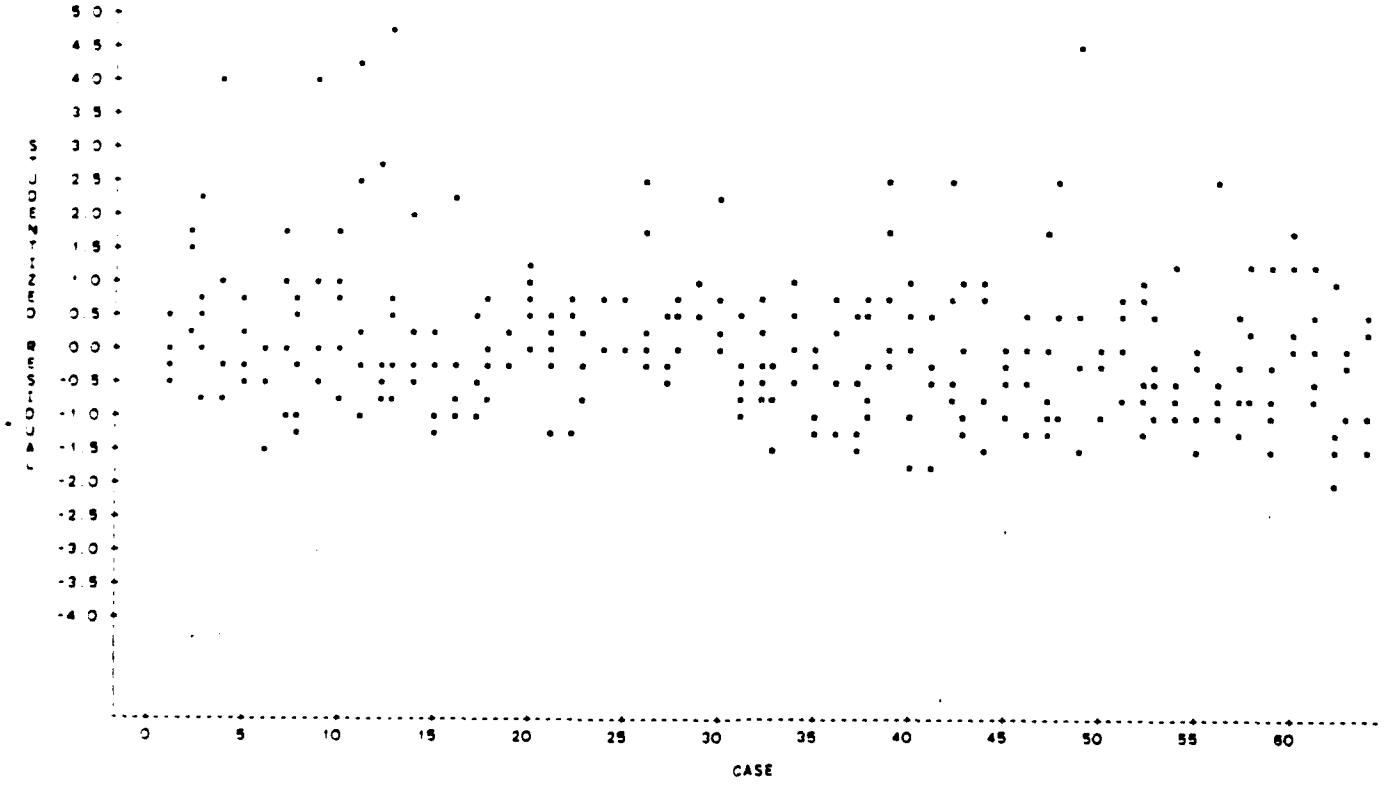
NOTE 2550 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 409 OBS HIDDEN

Studentized residuals versus predicted value of plasma epinephrine concentration.



NOTE 1260 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 50 OBS HIDDEN

Studentized residuals versus animal ID number (sham-exposure group).



NOTE 1290 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 37 OBS HIDDEN

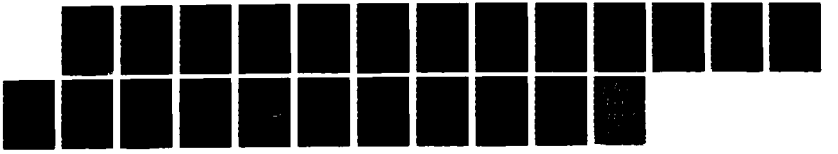
Studentized residuals versus animal ID number (exposure group).

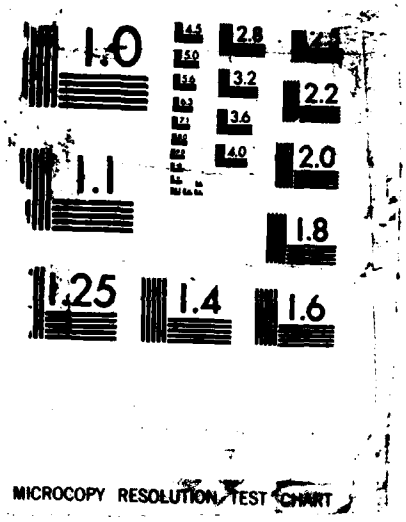
APPENDIX L

RAW DOPAMINE DATA SPREADSHEETS

AD-A188 255 LONG-TERM BIOEFFECTS OF 435-MHZ RADIOFREQUENCY RADIATION ON SELECTED BLOO (U) GEORGIA TECH RESEARCH INST ATLANTA V P POPOVIC ET AL AUG 87 2/2

UNCLASSIFIED USAFSAM-TR-87-11 F33615-83-K-0600 F/G 6/5 NL




1.0
1.1
1.25
1.4
1.6
1.8
2.0
2.2
2.8
3.2
3.6
4.0
MICROCOPY RESOLUTION TEST CHART

DA control I

Rat #	Group	-3WK	-2WK	0WK	TIME 1WK	2WK	3WK	4WK	5WK	6WK	7WK	8WK	9WK	10WK	11WK	12WK	13WK	14WK	15WK	16WK	17WK	18WK	19WK	20WK	21WK	22WK	23WK	24WK	+2	+5
1		31		65	58					18				57						30										
2		107		161	103					16				-						81										
3		-		64	22					4				-						37										
4		103		81	19					27				14						14										
5		160		71	65					-				59						19										
6		18		44	5					34				-						15										
7		86		120	44					6				59						24										
8		121		101	113					10				-						44										
9		16		42		61					-						47					10								
10		-		6		-					21						-					24								
11		61		41		18					27						-					15								
12		32		19		-					19						59					22								
13		84		23		22 21					36						31					37								

DA control II

Rat #	Group	-3WK	-2WK	0WK	TIME 1WK	2WK	3WK	4WK	5WK	6WK	7WK	8WK	9WK	10WK	11WK	12WK	13WK	14WK	15WK	16WK	17WK	18WK	19WK	20WK	21WK	22WK	23WK	24WK	+2	+5
14			160	84		18					19					160						91								
15			56	79		40					41					-						70								
16			43	-		31					37					20						21								
17			71	-		22					19					-						55								
18			95	60		22					-					13						62								
19		29		35		-					16					-						14								
20		-		35		19					14					28						20								
21		201		60		41					113					19						11								
22		19		84			-						20					-					7							
23		102		-			23						22					25					38							
24		48		61			20						-					-					21							
25		42		29			-						26					122					65							
26		36		18			18						19					12					20							

DA control III

Rat #	Group	-3HR	-2HR	0HR	TIME 1HR	2HR	3HR	4HR	5HR	6HR	7HR	8HR	9HR	10HR	11HR	12HR	13HR	14HR	15HR	16HR	17HR	18HR	19HR	20HR	21HR	22HR	23HR	24HR	+2	+5
27		44		91			32				34							17				—								
28		27		49			61				24							—				45								
29		61		—			27				40							31				27								
30		18		38			44				61							—				14								
31		41		38			48				7							44				8								
32		44		47			—				64						31					12								
33		29		—			38				37						—					—								
34		—		44	62							9					22					16								
35			—	64	6							46					—					44								
36			81	—	18							46					31					70								
37			56	53	43							—					42					11								
38			—	40	8							31					—					14								
39			44	61	25							31					—					—								

DA control IV

Rat #	Group	-3HR	-2HR	0HR	TIME 1HR	2HR	3HR	4HR	5HR	6HR	7HR	8HR	9HR	10HR	11HR	12HR	13HR	14HR	15HR	16HR	17HR	18HR	19HR	20HR	21HR	22HR	23HR	24HR	+2	+5
40		—		61		113					24				24					45										
41		—		35		—					41				—					14										
42		61		114	61						—				24					—										
43		44		91	9						15				—					27										
44		—		26	—						43				34					18										
45		39		—		41					64				41					—										
46			29	113	—						21				41					25										
47			61	—	31						12				—					15										
48			—	75			70					43				—						13								
49			39	61			—					86			95						70								
50			42	48			29					—			41						44								
51			27	92			—					—			31						20								
52			—	48			18					29			—						41								

DA control V

Rat #	Group	-3HR	-2HR	0HR	TIME 1HR	2HR	3HR	4HR	5HR	6HR	7HR	8HR	9HR	10HR	11HR	12HR	13HR	14HR	15HR	16HR	17HR	18HR	19HR	20HR	21HR	22HR	23HR	24HR	+2	+3
53		-		156			42				63					114						-								
54		43		64			-				35					-						29								
55		141		14			24				-					61						34								
56		-		40			65				24					51						-								
57		61		62			-				46					12						16								
58		42		-			18				50					104						83								
59		18	47				14				-					74						48								
60		-	55				76				95					14						40								
61		44	118			78	[illegible]				68					-					23									
62		35	112			46					63					45					-									
63		-	47			-					50					62					44									
64		60	21			29					[illegible]					15					70									
											88																			

DA MW I

Rat #	Group	-3HR	-2HR	0HR	TIME 1HR	2HR	3HR	4HR	5HR	6HR	7HR	8HR	9HR	10HR	11HR	12HR	13HR	14HR	15HR	16HR	17HR	18HR	19HR	20HR	21HR	22HR	23HR	24HR	+2	+3
1		-		70	78					41				-								16								
2		26		122	16					-				38								14								
3		40		-	63					24				28								23								
4		46		26	-					35				-								30								
5		-		61	14					23				40								-								
6		58		91	-					14				53								-								
7		30		-	24					40				-								32								
8		-		114	18					-				12								28								
9			57	44		-					38					19							-							
10			-	38	41						-					32							23							
11			48	88		-					61					21							23							
12			-	44	27						36					-							-							
13			-	-		61					16					20							16							

DA MW II

Rat #	Group	-3WK	-2WK	CWK	TIME 1WK	2WK	3WK	4WK	5WK	6WK	7WK	8WK	9WK	10WK	11WK	12WK	13WK	14WK	15WK	16WK	17WK	18WK	19WK	20WK	21WK	22WK	23WK	24WK	+2	+5
14		-	50			40				-	4			40								27								
15		60	41			91				27				-								37								
16		231	-			18				-				10								-								
17		-	36			19				4				41								15								
18		39	64			-				3				-								-								
19		-	186			8				15				20								21								
20		44	-			36				-				20								8								
21		60	111			-				18				-								34								
22		-	132				48				11							11					-							
23		28	-				65				6							37					24							
24		14	47				60				-							20					16							
25		-	20				27				20							-					16							
26		48	20				27				14							19					29							

DA MW II

Rat #	Group	-3WK	-2WK	CWK	TIME 1WK	2WK	3WK	4WK	5WK	6WK	7WK	8WK	9WK	10WK	11WK	12WK	13WK	14WK	15WK	16WK	17WK	18WK	19WK	20WK	21WK	22WK	23WK	24WK	+2	+5
27		38		65			21				10						36	30				32								
28		62		126			-				20						62	-				21								
29		-		32			19				-						52	20				16								
30		84		64			-				19							-				40								
31		-		23			41				19							61				23								
32		-		16			40				70							20				-								
33		19		41	-							7					-					14								
34		-		42	19							-					12				41	-								
35			56	-	31							27					-					11								
36			-	104	20							-					18					12								
37			14	-	22							18					-					8								
38			18	71	-							14					19					24								
39			155	80	24							13					-					12								

DA MW IV

Rat #	Group	-3WK	-2WK	0WK	TIME 1WK	2WK	3WK	4WK	5WK	6WK	7WK	8WK	9WK	10WK	11WK	12WK	13WK	14WK	15WK	16WK	17WK	18WK	19WK	20WK	21WK	22WK	23WK	24WK	+2	+5
46		69		83	x						19				14					21										
41		107		60	-						64				-					21										
42		43		-	8						23				14					-										
43		-		71	-						23				-					16										
44		82		37	24						-				26					14										
45		36		33	21						-				21					27										
46			52	-	-	34					12				17					-										
47			73	58		16						12				-					9	8								
48			-	76		21						17				25					23	20								
49			152	85		-						-				17					12	-								
50			44	76		34						-				21					18	18								
51			96	75		18						23				6					16	7								
52			-	14		-						16				12					4	-								

DA MW V

Rat #	Group	-3WK	-2WK	0WK	TIME 1WK	2WK	3WK	4WK	5WK	6WK	7WK	8WK	9WK	10WK	11WK	12WK	13WK	14WK	15WK	16WK	17WK	18WK	19WK	20WK	21WK	22WK	23WK	24WK	+2	+5
53		111		70			-					21					31					21								
54		17		26			18					-					31					20								
55		-		58			-					16					-					-								
56		29		-			21					23					73					18								
57		-		38			-					23					-					24								
58		16		39			36					48					21					-								
59		157	-					8			12					24					18									
60		-	48					12			-					16					-									
61		40	52					-			22					-					25									
62		37	66					31			18					21					18									
63		82	-					20			34					11					23									
64		-	41					28			12					19					11									

APPENDIX M

DOPAMINE SAS FORMATTING PROGRAM

```
1          SAS(R) LOG  CMS SAS 5.16      VM/CMS CMS USER QSECLSB

NOTE: COPYRIGHT (C) 1984,1986 SAS INSTITUTE INC., CARY, N.C.  27511, U.S.A.
NOTE: CMS SAS RELEASE 5.16 AT GEORGIA INSTITUTE OF TECHNOLOGY (03559001).

NOTE: CPUID   VERSION = FF  SERIAL = 012242  MODEL = 4381 .

NOTE: SAS OPTIONS SPECIFIED ARE:
      LEAVE=0

  1 DATA TESTD;
  2 CMS FILEDEF X DISK DOPAMIN DAT A1;
  3 CMS FILEDEF 20 DISK DOPAMIN0 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
  4 CMS FILEDEF 21 DISK DOPAMIN1 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
  5 CMS FILEDEF 22 DISK DOPAMIN2 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
  6 CMS FILEDEF 23 DISK DOPAMIN3 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
  7 CMS FILEDEF 24 DISK DOPAMIN4 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
  8 CMS FILEDEF 25 DISK DOPAMIN5 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
  9 CMS FILEDEF 26 DISK DOPAMIN6 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
 10 CMS FILEDEF 27 DISK DOPAMIN7 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
 11 CMS FILEDEF 28 DISK DOPAMIN8 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
 12 ARRAY WEEK {24} WKN3 WKN2 MISSN1 WK0-WK20;
 13 KEEP X XSQR Y Z XZ XSQRZ CASE;
 14 INFILE X;
 15 INPUT CASE 1-3
 16       WKN3 5-7
 17       WKN2 9-11
 18       WK0 13-15
 19       WK1 17-19
 20       WK2 21-23
 21       WK3 25-27
 22       WK4 29-31
 23       WK5 33-35
 24       WK6 37-39
 25       WK7 41-43
 26       WK8 45-47
 27       WK9 49-51
 28       WK10 53-55
 29       WK11 57-59
 30       WK12 61-63
 31       WK13 65-67
 32       WK14 69-71
 33       WK15 73-75
 34       WK16 77-79
 35       WK17 81-83
 36       WK18 85-87
 37       WK19 89-91
 38       WK20 93-95
 39 ;
 40 MISSN1=.;
 41 IF CASE < 100 THEN Z = 0;
 42 IF CASE >= 100 THEN Z = 1;
 43 IF Z=1 THEN CASE=CASE-100;
 44 DO I = 1 TO 24;
 45 X = I-4; XSQR = X*X; XZ = X*Z; XSQRZ = X*X*Z; Y = WEEK {I};OUTPUT;
 46 END;


NOTE: INFILE X IS FILE DOPAMIN DAT A1
NOTE: 128 LINES WERE READ FROM INFILE X.
```

```
2          SAS(R) LOG  CMS SAS 5.16      VM/CMS CMS USER QSECLSB

NOTE: DATA SET WORK.TESTD HAS 3072 OBSERVATIONS AND 7 VARIABLES.
NOTE: THE DATA STATEMENT USED 0.58 SECONDS AND 252K.

 47 PROC CONTENTS;
NOTE: THE PROCEDURE CONTENTS USED 0.20 SECONDS AND 316K AND PRINTED PAGES 1 TO 2.

 48 PROC PRINTTO NEW UNIT=20;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 316K.

 49 PROC SORT OUT=SCTR;
 50      BY Z X Y;

NOTE: DATA SET WORK.SCTR HAS 3072 OBSERVATIONS AND 7 VARIABLES.
NOTE: THE PROCEDURE SORT USED 0.78 SECONDS AND 6908K.

 51 PROC SUMMARY;
 52      BY Z X;
 53      VAR Y;
 54      OUTPUT OUT=OVLMN MEAN=MEAN;
NOTE: THE DATA SET WORK.OVLMN HAS 48 OBSERVATIONS AND 5 VARIABLES.
NOTE: THE PROCEDURE SUMMARY USED 0.57 SECONDS AND 444K.

 55 DATA SDOPAMIN;
 56      SET SCTR OVLMN;
 57      BY Z;

NOTE: DATA SET WORK.SDOPAMIN HAS 3120 OBSERVATIONS AND 10 VARIABLES.
NOTE: THE DATA STATEMENT USED 0.57 SECONDS AND 316K.

 58 PROC PLOT NOLEGEND DATA=SDOPAMIN;
 59      BY Z;
 60      PLOT MEAN*X='X' Y*X='.' / HAXIS=-3 TO 20 BY 1 VAXIS=0 TO 100 BY 10 OVERLAY;
 61      TITLE 'DOPAMINE SCATTER DIAGRAM';
NOTE: THE PROCEDURE PLOT USED 0.66 SECONDS AND 444K AND PRINTED PAGES 3 TO 4.

 62 PROC PRINTTO NEW UNIT=21;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 316K.

 63 PROC PLOT NOLEGEND DATA=SDOPAMIN;
 64      PLOT MEAN*X='X' / HAXIS=-3 TO 20 BY 1 VAXIS=0 TO 100 BY 10;
 65      TITLE 'Mean Dopamine Concentration Versus Time';
NOTE: THE PROCEDURE PLOT USED 0.47 SECONDS AND 444K AND PRINTED PAGE 5.

 66 PROC PRINTTO NEW UNIT=22;
 67      TITLE 'CATECHOLAMINE ANALYSIS:  Dopamine';

NOTE: THE PROCEDURE PRINTTO USED 0.03 SECONDS AND 316K.

 68 PROC DATASETS;
 69
LIST OF MEMBERS BEFORE UPDATE OF DIRECTORY.
NAME     MEMTYPE             OBS  TRACKS PROT
OVLMN    /DATA                48       1
SCTR     /DATA              3072       1
SDOPAMIN/DATA               3120       1
TESTD    /DATA              3072       1
```

```
 69      DELETE SCTR;
 70      DELETE OVLMN;
LIST OF MEMBERS AFTER UPDATE OF DIRECTORY.
NAME    MEMTYPE            OBS  TRACKS PROT
SDOPAMIN/DATA             3120       1
TESTD   /DATA             3072       1
NOTE: THE PROCEDURE DATASETS USED 0.12 SECONDS AND 444K.

 71 PROC STEPWISE;
 72      MODEL Y = X XSQR Z XZ XSQRZ / SLENTRY=0.10 SLSTAY=0.10 STEPWISE MAXR;
NOTE: THE PROCEDURE STEPWISE USED 0.60 SECONDS AND 444K AND PRINTED PAGES 6 TO 9.

 73 PROC PRINTTO NEW UNIT=23;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 316K.

 74 PROC REG;
 75      MODEL Y = X XSQR XZ / PARTIAL;
 76      ID CASE;
NOTE: ACOV AND SPEC OPTION ONLY VALID WITH RAWDATA
NOTE: THE PROCEDURE REG USED 1.64 SECONDS AND 636K AND PRINTED PAGES 10 TO 14.

 77 PROC PRINTTO NEW UNIT=24;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 316K.

 78 PROC GLM;
 79      CLASS X Z;
 80      MODEL Y = X X*X X*Z;
NOTE: THE PROCEDURE GLM USED 3.20 SECONDS AND 1020K AND PRINTED PAGES 15 TO 16.

 81 PROC PRINTTO NEW UNIT=25;
 82 *-------------------------------------------------------------------*
 83 *                                                                   *
 84 *     to obtain tables listing the variance inflation factors,      *
 85 *     influence statistics, and tolerances, the following SAS       *
 86 *     statements were used in this partition:                       *
 87 *                                                                   *
 88 *     PROC REG;                                                     *
 89 *          MODEL Y = X XSQR XZ / TOL VIF INFLUENCE;                 *
 90 *          ID CASE;                                                 *
 91 *          OUTPUT OUT=RDOPAMIN P=PREDICT R=RESID STUDENT=STUDENT;       *
 92 *                                                                   *
 93 *-------------------------------------------------------------------*;

NOTE: THE PROCEDURE PRINTTO USED 0.04 SECONDS AND 316K.

 94 PROC REG;
 95      MODEL Y = X XSQR XZ / I SS1 SS2 STB COVB CORRB SEQB COLLIN
 96                            COLLINOINT ACOV P R CLM;
 97      ID CASE;
 98      OUTPUT OUT=RDOPAMIN P=PREDICT R=RESID STUDENT=STUDENT;
NOTE: THE DATA SET WORK.RDOPAMIN HAS 3120 OBSERVATIONS AND 13 VARIABLES.
NOTE: THE PROCEDURE REG USED 7.33 SECONDS AND 636K AND PRINTED PAGES 17 TO 83.

 99 PROC PRINTTO NEW UNIT=26:

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 316K.
```

```
100 PROC PLOT DATA=RDOPAMIN;
101       PLOT RESID*X='*' / HAXIS=-3 TO 20 BY 1 VAXIS=-125 TO 125 BY 25;
102       PLOT RESID*PREDICT='*' / HAXIS=15 TO 65 BY 5 VAXIS=-125 TO 125 BY 25;
103       PLOT STUDENT*X='*' / HAXIS=-3 TO 20 BY 1 VAXIS=-2 TO 6 BY 0.5;
104       PLOT STUDENT*PREDICT='*' / HAXIS=15 TO 65 BY 5 VAXIS=-2 TO 6 BY 0.5;
105       TITLE 'DOPAMINE RESIDUAL PLOTS';
NOTE: THE PROCEDURE PLOT USED 0.96 SECONDS AND 444K AND PRINTED PAGES 84 TO 87.

106 PROC PRINTTO NEW UNIT=27;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 316K.

107 PROC PLOT DATA=RDOPAMIN;
108       BY Z;
109       PLOT RESID*CASE='*' / HAXIS=0 TO 65 BY 5 VAXIS=-125 TO 125 BY 25;
110       PLOT STUDENT*CASE='*' / HAXIS=0 TO 65 BY 5 VAXIS=-2 TO 6 BY 0.5;
111       TITLE 'DOPAMINE RESIDUAL PLOTS';
NOTE: THE PROCEDURE PLOT USED 0.79 SECONDS AND 444K AND PRINTED PAGES 88 TO 91.

112 PROC PRINTTO NEW UNIT=28;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 316K.

113 PROC AUTOREG;
114       TITLE 'Dopamine Autoregressive Models';
115       MODEL Y = X XSQR XZ / COEF CORRB COVB BACKSTEP;
116       MODEL Y = X XSQR XZ / NLAG=1 COEF CORRB COVB BACKSTEP;
117       MODEL Y = X XSQR XZ / NLAG=2 COEF CORRB COVB BACKSTEP;
118       MODEL Y = X XSQR XZ / NLAG=3 COEF CORRB COVB BACKSTEP;
119       MODEL Y = X XSQR XZ / NLAG=4 COEF CORRB COVB BACKSTEP;
NOTE: THE PROCEDURE AUTOREG USED 6.82 SECONDS AND 444K AND PRINTED PAGES 92 TO 104.
NOTE: SAS USED 6908K MEMORY.

NOTE: SAS INSTITUTE INC.
      SAS CIRCLE
      PO BOX 8000
      CARY, N.C. 27511-8000
```

APPENDIX N

STEPWISE AND MAXIMUM R^2 REGRESSION PROCEDURES USED TO BUILD DOPAMINE MODEL

CATECHOLAMINE ANALYSIS: Dopamine 9:42 WEDNESDAY, JULY 15, 1987

STEPWISE REGRESSION PROCEDURE FOR DEPENDENT VARIABLE Y

WARNING: 2540 OBSERVATIONS DELETED DUE TO MISSING VALUES.

STEP 1 VARIABLE X ENTERED R SQUARE = 0.13383387 C(P) = 35.64759543

	DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
REGRESSION	1	79084.01924111	79084.01924111	89.31	0.0001
ERROR	578	511827.81524165	885.51525128		
TOTAL	579	590911.83448276			

	B VALUE	STD ERROR	TYPE II SS	F	PROB>F
INTERCEPT	50.88462452				
X	-1.61034271	0.17040093	79084.01924111	89.31	0.0001

BOUNDS ON CONDITION NUMBER: 1, 1

STEP 2 VARIABLE XSQR ENTERED R SQUARE = 0.16378089 C(P) = 16.50035676

	DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
REGRESSION	2	96780.06684698	48390.03342349	56.51	0.0001
ERROR	577	494131.76763578	856.38087978		
TOTAL	579	590911.83448276			

	B VALUE	STD ERROR	TYPE II SS	F	PROB>F
INTERCEPT	51.16621035				
X	-3.60718727	0.47015576	50410.47786297	58.86	0.0001
XSQR	0.13229708	0.02910352	17696.04760587	20.66	0.0001

BOUNDS ON CONDITION NUMBER: 7.871703, 31.48681

STEP 3 VARIABLE XZ ENTERED R SQUARE = 0.18228629 C(P) = 5.43267906

	DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
REGRESSION	3	107715.12320433	35905.04106811	42.80	0.0001
ERROR	576	483196.71127843	838.88317930		
TOTAL	579	590911.83448276			

	B VALUE	STD ERROR	TYPE II SS	F	PROB>F
INTERCEPT	51.19300509				
X	-3.14137153	0.48288295	35502.28830246	42.32	0.0001
XSQR	0.13040108	0.02880945	17186.75431622	20.49	0.0001
XZ	-0.92081500	0.25504253	10935.05635735	13.04	0.0003

BOUNDS ON CONDITION NUMBER: 8.476848, 53.65372

NO OTHER VARIABLES MET THE 0.1000 SIGNIFICANCE LEVEL FOR ENTRY INTO THE MODEL.

CATECHOLAMINE ANALYSIS: Dopamine 9:42 WEDNESDAY, JULY 15, 1987

SUMMARY OF STEPWISE REGRESSION PROCEDURE FOR DEPENDENT VARIABLE Y

STEP	VARIABLE ENTERED	VARIABLE REMOVED	NUMBER IN	PARTIAL R**2	MODEL R**2	C(P)	F	PROB>F
1	X		1	0.1338	0.1338	35.6476	89.3085	0.0001
2	XSQR		2	0.0299	0.1638	16.5004	20.6638	0.0001
3	XZ		3	0.0185	0.1823	5.4327	13.0353	0.0003

MAXIMUM R-SQUARE IMPROVEMENT FOR DEPENDENT VARIABLE Y

WARNING: 2540 OBSERVATIONS DELETED DUE TO MISSING VALUES.

STEP 1 VARIABLE X ENTERED R SQUARE = 0.13383387 C(P) = 35.64759543

	DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
REGRESSION	1	79084.01924111	79084.01924111	89.31	0.0001
ERROR	578	511827.81524165	885.51525128		
TOTAL	579	590911.83448276			

	B VALUE	STD ERROR	TYPE II SS	F	PROB>F
INTERCEPT	50.88462452				
X	-1.61034271	0.17040093	79084.01924111	89.31	0.0001

BOUNDS ON CONDITION NUMBER: 1, 1

THE ABOVE MODEL IS THE BEST 1 VARIABLE MODEL FOUND.

STEP 2 VARIABLE XSQR ENTERED R SQUARE = 0.16378089 C(P) = 16.50035676

	DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
REGRESSION	2	96780.06684698	48390.03342349	56.51	0.0001
ERROR	577	494131.76763578	856.38087978		
TOTAL	579	590911.83448276			

	B VALUE	STD ERROR	TYPE II SS	F	PROB>F
INTERCEPT	51.16621035				
X	-3.60718727	0.47015576	50410.47786297	58.86	0.0001
XSQR	0.13229708	0.02910352	17696.04760587	20.66	0.0001

BOUNDS ON CONDITION NUMBER: 7.871703, 31.48681

THE ABOVE MODEL IS THE BEST 2 VARIABLE MODEL FOUND.

STEP 3 VARIABLE XZ ENTERED R SQUARE = 0.18228629 C(P) = 5.43267906

	DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
REGRESSION	3	107715.12320433	35905.04106811	42.80	0.0001
ERROR	576	483196.71127843	838.88317930		
TOTAL	579	590911.83448276			

	B VALUE	STD ERROR	TYPE II SS	F	PROB>F
INTERCEPT	51.19300509				
X	-3.14137153	0.48288295	35502.28830246	42.32	0.0001
XSQR	0.13040108	0.02880945	17186.75431622	20.49	0.0001
XZ	-0.92081500	0.25504253	10935.05635735	13.04	0.0003

BOUNDS ON CONDITION NUMBER: 8.476848, 53.65372

MAXIMUM R-SQUARE IMPROVEMENT FOR DEPENDENT VARIABLE Y

THE ABOVE MODEL IS THE BEST 3 VARIABLE MODEL FOUND.

STEP 4 VARIABLE Z ENTERED R SQUARE = 0.18561951 C(P) = 5.07890681

	DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
REGRESSION	4	109684.76408667	27421.19102167	32.76	0.0001
ERROR	575	481227.07039609	836.91664417		
TOTAL	579	590911.83448276			

	B VALUE	STD ERROR	TYPE II SS	F	PROB>F
INTERCEPT	53.46801950				
X	-3.29252492	0.49227772	37438.63316655	44.73	0.0001
XSQR	0.13025415	0.02877582	17147.85500401	20.49	0.0001
Z	-4.80630860	3.13299159	1969.64088234	2.35	0.1256
XZ	-0.59459324	0.33183311	2687.09295880	3.21	0.0737

BOUNDS ON CONDITION NUMBER: 8.830601, 84.0164

THE ABOVE MODEL IS THE BEST 4 VARIABLE MODEL FOUND.

STEP 5 VARIABLE XSQRZ ENTERED R SQUARE = 0.18714737 C(P) = 6.00000000

	DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
REGRESSION	5	110587.59525974	22117.51905195	26.43	0.0001
ERROR	574	480324.23922302	836.80181049		
TOTAL	579	590911.83448276			

	B VALUE	STD ERROR	TYPE II SS	F	PROB>F
INTERCEPT	53.41128854				
X	-2.85185028	0.64984281	16116.08025819	19.26	0.0001
XSQR	0.10118340	0.04014020	5317.18959525	6.35	0.0120
Z	-4.67847901	3.13519295	1863.38859502	2.23	0.1362
XZ	-1.49685016	0.92985381	2168.45252801	2.59	0.1080
XSQRZ	0.05979800	0.05756979	902.83117307	1.08	0.2994

BOUNDS ON CONDITION NUMBER: 20.43339, 361.1462

THE ABOVE MODEL IS THE BEST 5 VARIABLE MODEL FOUND.

APPENDIX O

DOPAMINE LACK-OF-FIT TEST

CATECHOLAMINE ANALYSIS: Dopamine 9:42 WEDNESDAY, JULY 15, 1987

GENERAL LINEAR MODELS PROCEDURE

DEPENDENT VARIABLE: Y

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PR > F	R-SQUARE
MODEL	37	149717.57206551	4046.42086664	4.97	0.0001	0.253367
ERROR	542	441194.26241725	814.01155428		ROOT MSE	
CORRECTED TOTAL	579	590911.83448276			28.53088772	

SOURCE	DF	TYPE I SS	F VALUE	PR > F	DF	TYPE III SS	F VALUE
X	19	128211.55135535	8.29	0.0001	19	124070.95712755	8.02
X*Z	18	21506.02071016	1.47	0.0958	18	21506.02071016	1.47

this term is solely a measure of sum-of-squares pure error.

116

Partitioning SS_E into SS_{pe} and SS_{lof}

$SS_E = 483196.71$ $\quad df = 576$

$SS_{pe} = 441194.26$ $\quad df = 542$

$SS_{lof} = 42002.45$ $\quad df = 34$

$MS_{lof} = 1235.37$

$MS_{pe} = 814.01$

$$F_o = \frac{MS_{lof}}{MS_{pe}} = 1.5176$$

$F_{0.10,34,542} \sim 1.38$

CATECHOLAMINE ANALYSIS: Dopamine

ANALYSIS OF VARIANCE

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PROB>F
MODEL	3	107715.12	35905.04107	42.801	0.0001
ERROR	576	483196.71	838.88318		
C TOTAL	579	590911.83			

ROOT MSE	28.96348	R-SQUARE	0.1823
DEP MEAN	41.14483	ADJ R-SQ	0.1780
C.V.	70.39398		

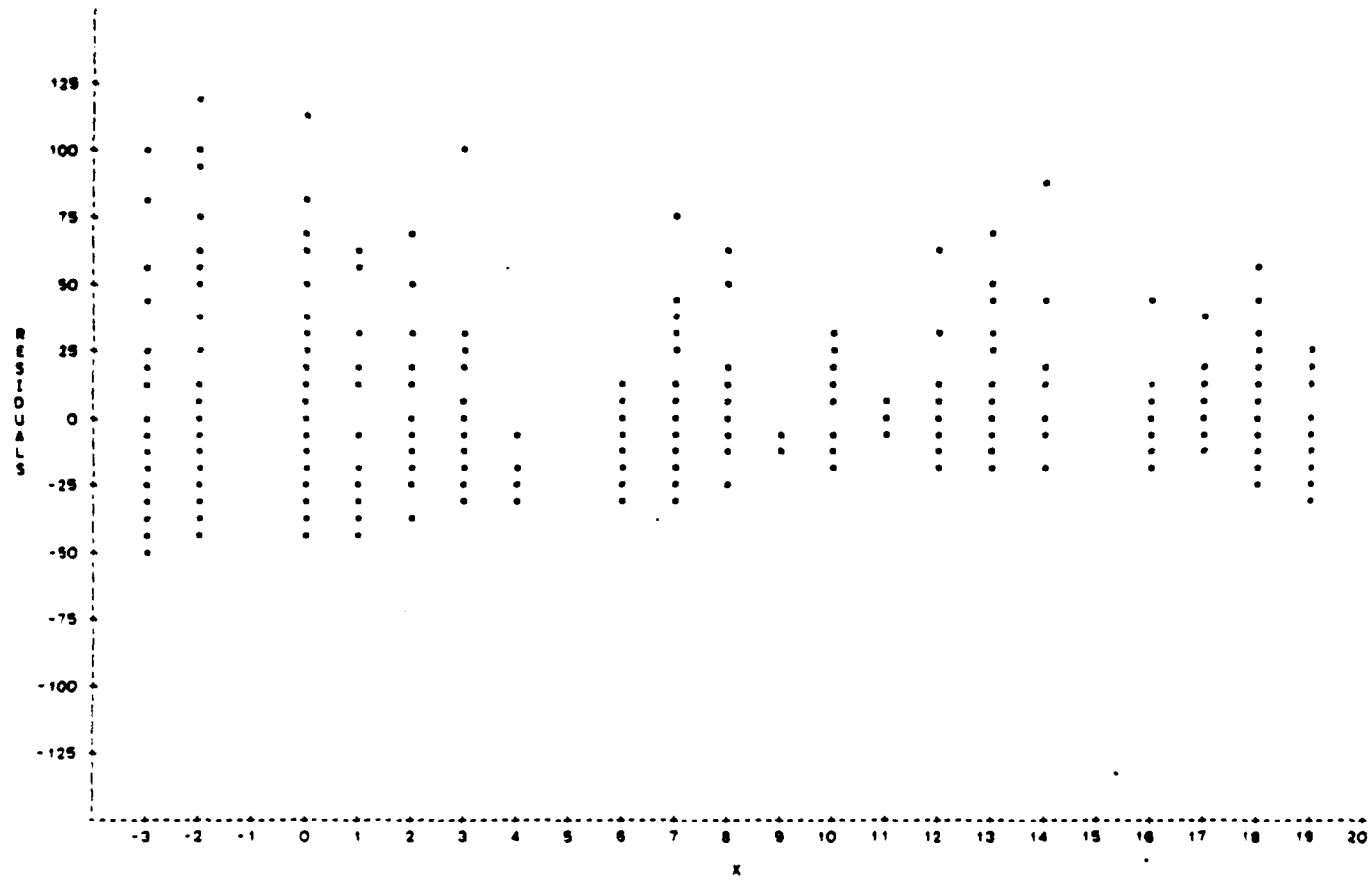
PARAMETER ESTIMATES

VARIABLE	DF	PARAMETER ESTIMATE	STANDARD ERROR	T FOR HO: PARAMETER=0	PROB > |T|
INTERCEP	1	51.19300509	1.56730010	32.663	0.0001
X	1	-3.14137153	0.48288295	-6.505	0.0001
XSQR	1	0.13040108	0.02880945	4.526	0.0001
XZ	1	-0.92081500	0.25504253	-3.610	0.0003

this term contains both sum-of-squares pure error and sum-of-squares lack-of-fit.

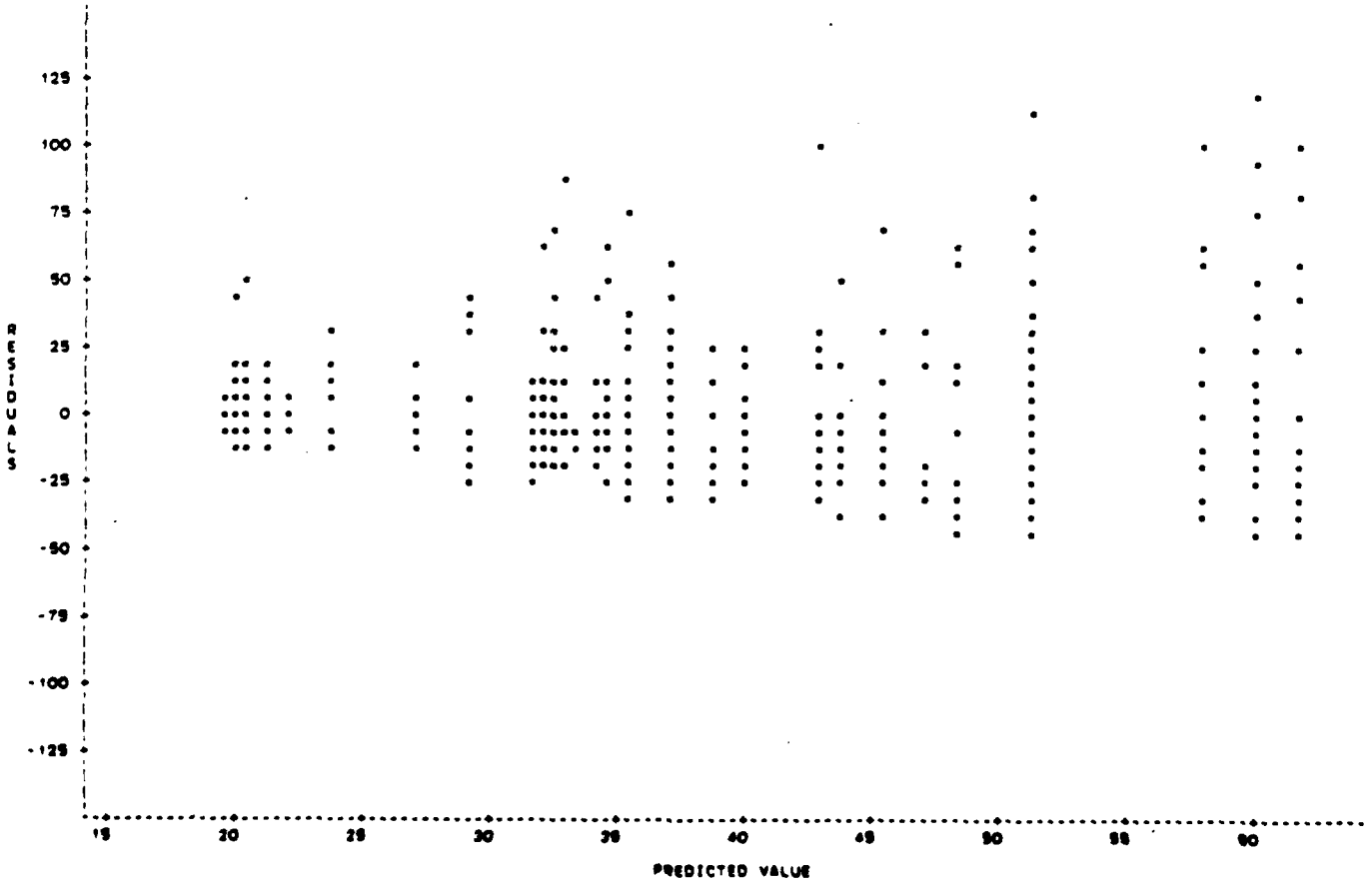
APPENDIX P

DOPAMINE RESIDUAL PLOTS



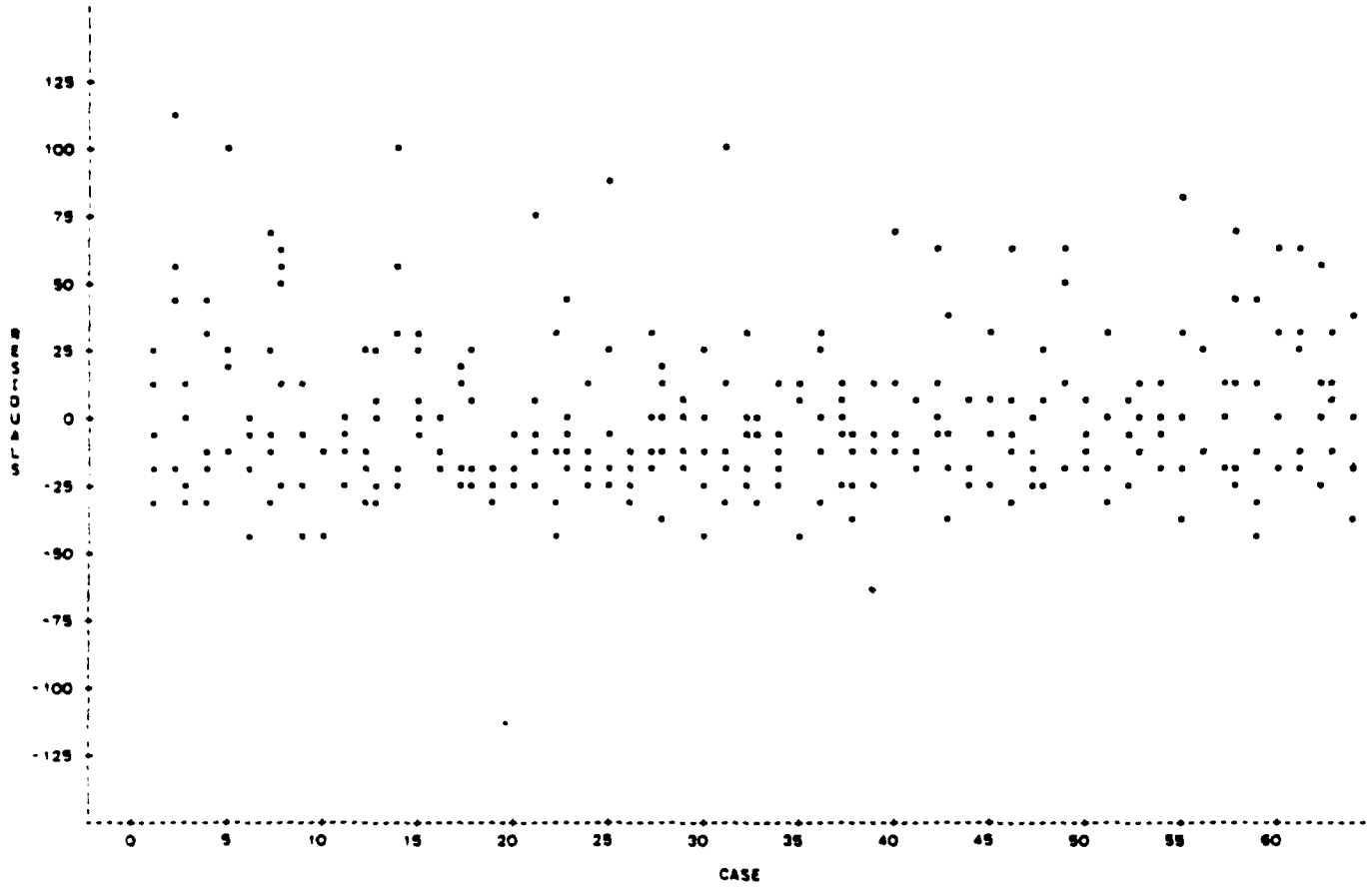
NOTE: 2544 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 381 OBS HIDDEN

Residuals versus time.



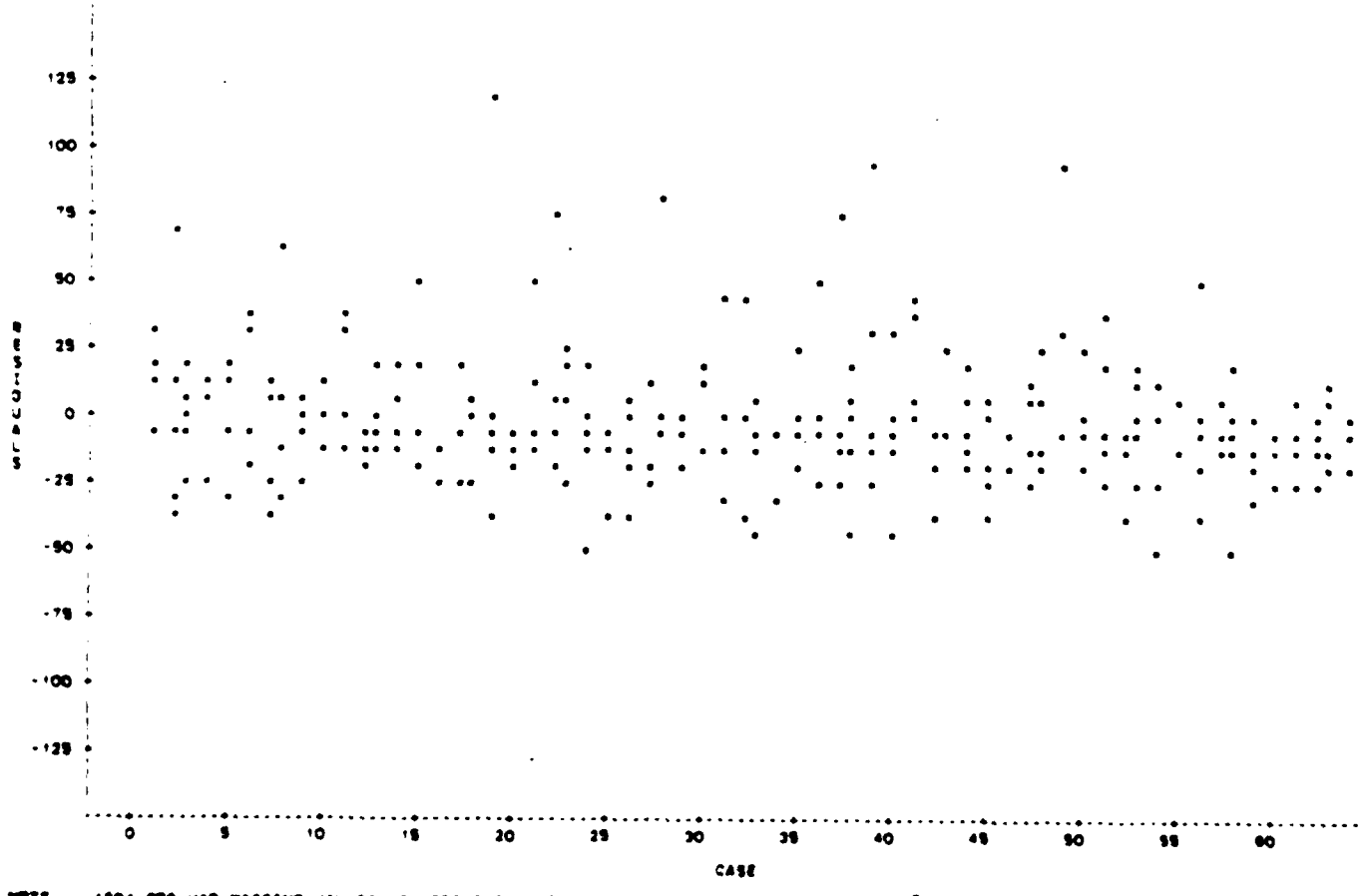
NOTE 2544 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 330 OBS HIDDEN

Residuals versus predicted value of plasma dopamine concentration.



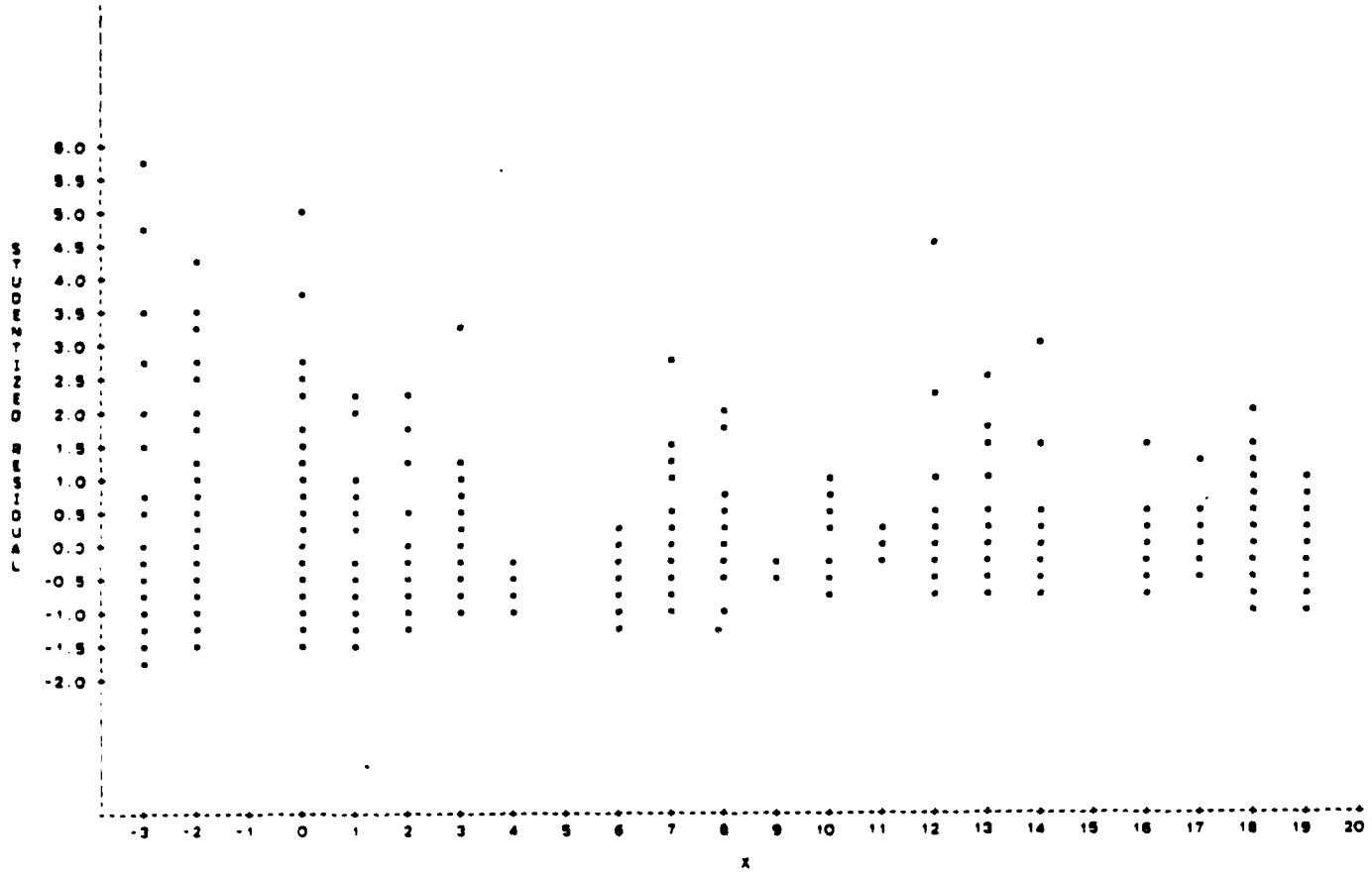
NOTE 1260 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 37 OBS HIDDEN

Residuals versus animal ID number (sham-exposure group).



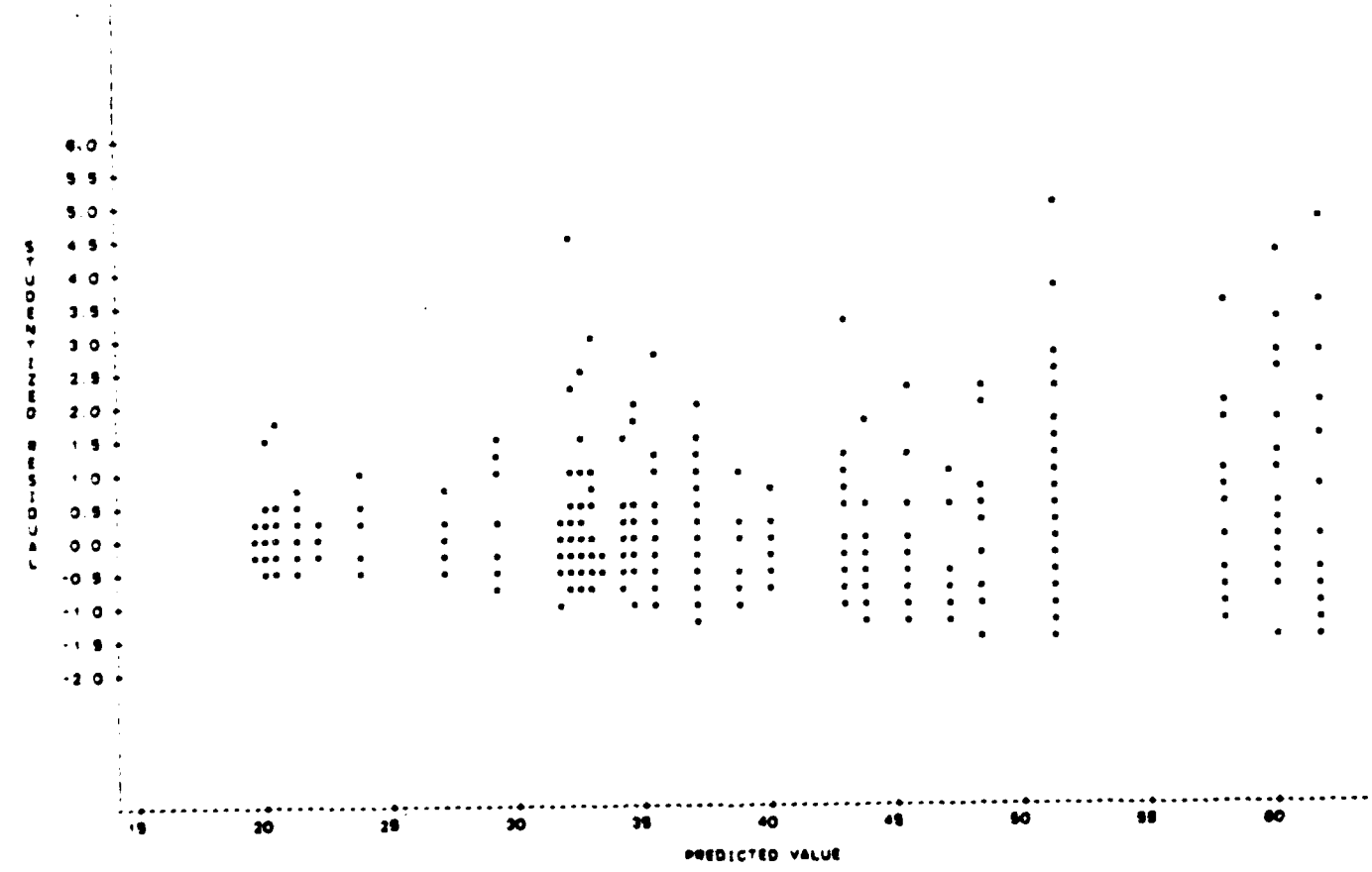
NOTE 1284 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 34 OBS HIDDEN

Residuals versus animal ID number (exposure group).



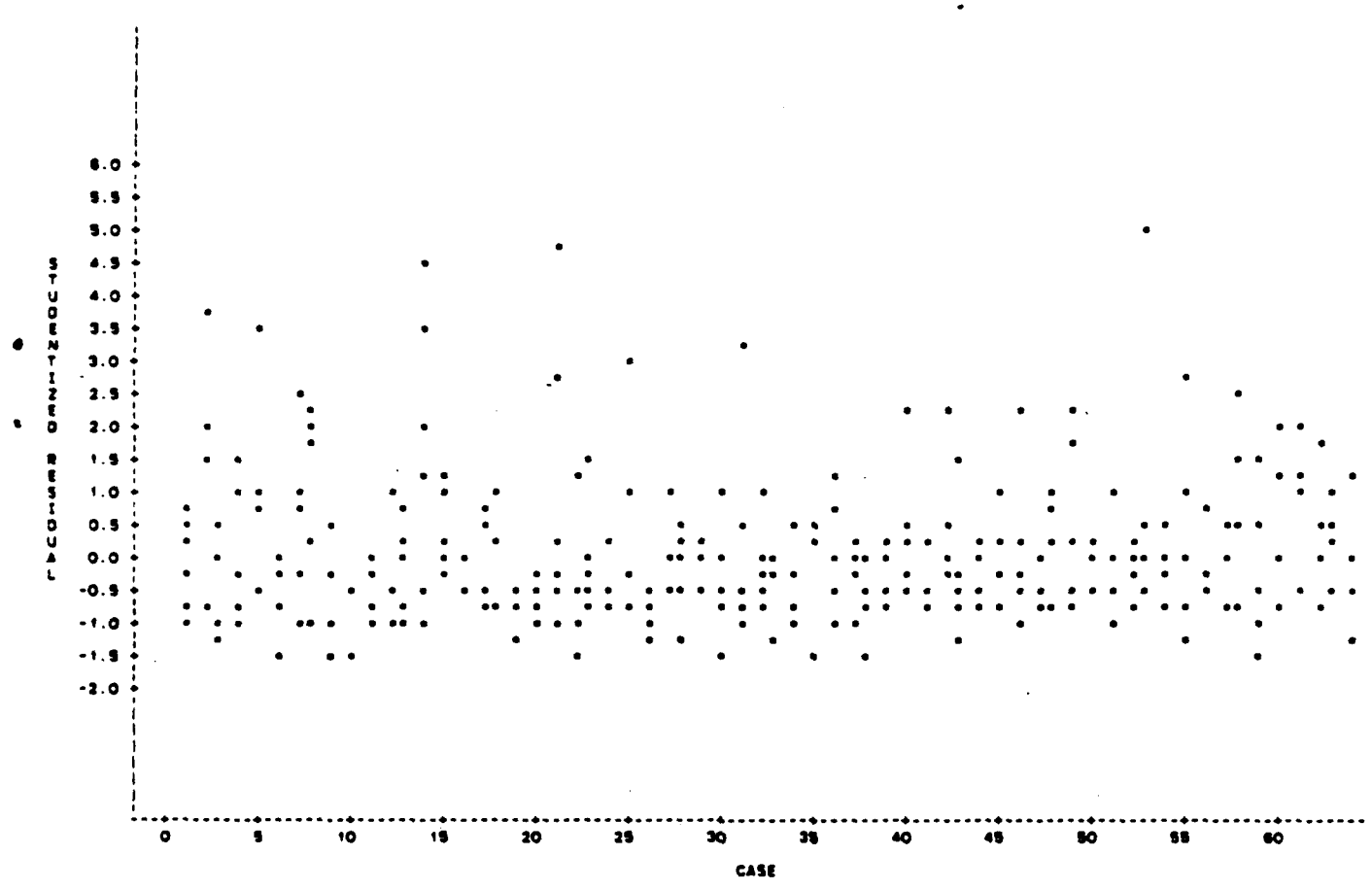
NOTE 2940 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 389 OBS HIDDEN

Studentized residuals versus time.



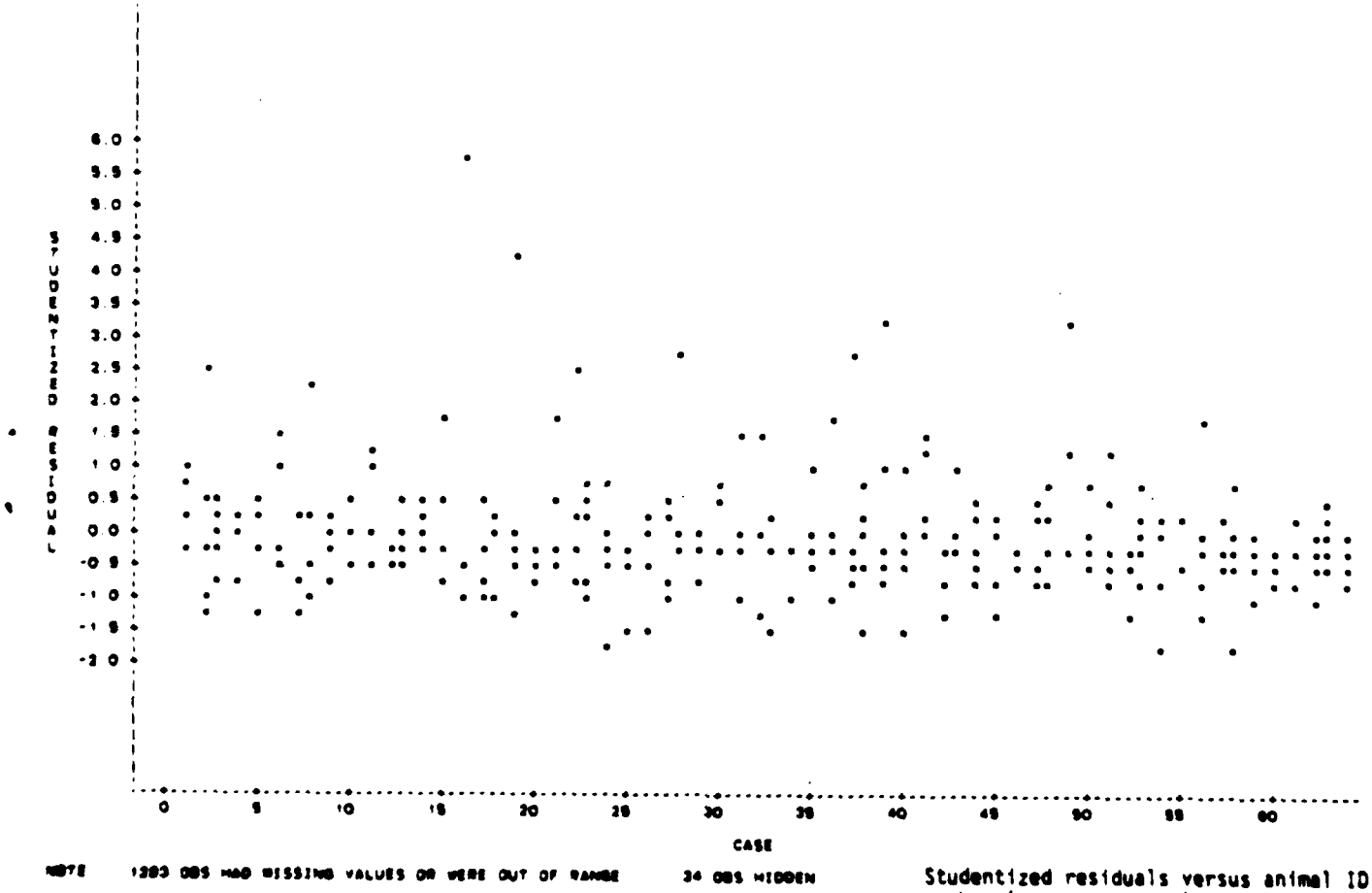
NOTE 2940 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 348 OBS HIDDEN

Studentized residuals versus predicted value of plasma dopamine concentration.



NOTE: 1257 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 41 OBS HIDDEN

Studentized residuals versus animal ID number (sham-exposure group).



NOTE: 1283 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 34 OBS HIDDEN

Studentized residuals versus animal ID number (exposure group).

END

Feb.

1988

DTIC